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NEWS 7	Mar 04	SDI PACKAGE for monthly delivery of multifile SDI results
NEWS 8	Mar 24	PATDPAFULL now available on STN
NEWS 9	Mar 24	Additional information for trade-named substances without structures available in REGISTRY
NEWS 10	Apr 11	Display formats in DGENE enhanced
NEWS 11	Apr 14	MEDLINE Reload
NEWS 12	Apr 17	Polymer searching in REGISTRY enhanced
NEWS 13	AUG 22	Indexing from 1927 to 1936 added to records in CA/CAPLUS
NEWS 14	Apr 21	New current-awareness alert (SDI) frequency in WPIDS/WPINDEX/WPIX
NEWS 15	Apr 28	RDISCLOSURE now available on STN
NEWS 16	May 05	Pharmacokinetic information and systematic chemical names added to PHAR
NEWS 17	May 15	MEDLINE file segment of TOXCENTER reloaded
NEWS 18	May 15	Supporter information for ENCOMPPAT and ENCOMPLIT updated
NEWS 19	May 19	Simultaneous left and right truncation added to WSCA
NEWS 20	May 19	RAPRA enhanced with new search field, simultaneous left and right truncation
NEWS 21	Jun 06	Simultaneous left and right truncation added to CBNB
NEWS 22	Jun 06	PASCAL enhanced with additional data
NEWS 23	Jun 20	2003 edition of the FSTA Thesaurus is now available
NEWS 24	Jun 25	HSDB has been reloaded
NEWS 25	Jul 16	Data from 1960-1976 added to RDISCLOSURE
NEWS 26	Jul 21	Identification of STN records implemented
NEWS 27	Jul 21	Polymer class term count added to REGISTRY
NEWS 28	Jul 22	INPADOC: Basic index (/BI) enhanced; Simultaneous Left and Right Truncation available
NEWS 29	AUG 05	New pricing for EUROPATFULL and PCTFULL effective August 1, 2003
NEWS 30	AUG 13	Field Availability (/FA) field enhanced in BEILSTEIN
NEWS 31	AUG 15	PATDPAFULL: one FREE connect hour, per account, in September 2003
NEWS 32	AUG 15	PCTGEN: one FREE connect hour, per account, in September 2003
NEWS 33	AUG 15	RDISCLOSURE: one FREE connect hour, per account, in September 2003
NEWS 34	AUG 15	TEMA: one FREE connect hour, per account, in September 2003
NEWS 35	AUG 18	Data available for download as a PDF in RDISCLOSURE
NEWS 36	AUG 18	Simultaneous left and right truncation added to PASCAL
NEWS 37	AUG 18	FROSTI and KOSMET enhanced with Simultaneous Left and Right Truncation
NEWS 38	AUG 18	Simultaneous left and right truncation added to ANABSTR

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 NEWS EXPRESS  April 4 CURRENT WINDOWS VERSION IS V6.01a, CURRENT
               MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),
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FILE COVERS 1971 TO PATENT PUBLICATION DATE: 26 Aug 2003 (20030826/PD)
FILE LAST UPDATED: 26 Aug 2003 (20030826/ED)
HIGHEST GRANTED PATENT NUMBER: US6611958
HIGHEST APPLICATION PUBLICATION NUMBER: US2003159190
CA INDEXING IS CURRENT THROUGH 26 Aug 2003 (20030826/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 26 Aug 2003 (20030826/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Jun 2003
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```
=> s thiazolidine and pyridyl and methyl and benzyl and diabetes
          4534 THIAZOLIDINE
         40027 PYRIDYL
        408264 METHYL
        140884 BENZYL
         27133 DIABETES
L1         342 THIAZOLIDINE AND PYRIDYL AND METHYL AND BENZYL AND DIABETES

=> s l1 and glimepiride
           346 GLIMEPIRIDE
L2          31 L1 AND GLIMEPIRIDE

=> s l2 and l2 (w) mg
       3026649 12
        318002 MG
         10032 12 (W) MG
L3          15 L2 AND 12 (W) MG

=> d l3 1-15 bib, ab, kwic,

L3   ANSWER 1 OF 15  USPATFULL on STN
AN     2003:226364  USPATFULL
TI     Melanin-concentrating hormone antagonist
IN     Ishihara, Yuji, Itami-shi, JAPAN
       Terauchi, Jun, Ikeda-shi, JAPAN
       Suzuki, Nobuhiro, Minoo-shi, JAPAN
       Takekawa, Shiro, Nishinomiya-shi, JAPAN
       Aso, Kazuyoshi, Takatsuki-shi, JAPAN
PI     US 2003158177      A1   20030821
AI     US 2002-276288     A1   20021112 (10)
       WO 2001-JP4015          20010515
PRAI   JP 2000-148674      20000516
       JP 2001-116219      20010413
DT     Utility
FS     APPLICATION
LREP   TAKEDA PHARMACEUTICALS NORTH AMERICA, INC, INTELLECTUAL PROPERTY
       DEPARTMENT, 475 HALF DAY ROAD, SUITE 500, LINCOLNSHIRE, IL, 60069
CLMN   Number of Claims: 40
ECL    Exemplary Claim: 1
DRWN   No Drawings
LN.CNT 7199
AB     A melanin-concentrating hormone antagonist comprising a compound of the
       formula:   ##STR1##

       wherein R is hydrogen atom or a cyclic group which may be substituted; X
       is a bond or a spacer having a main chain of 1 to 10 atoms; Y is a
       spacer having a main chain of 1 to 6 atoms; ring A is benzene ring which
       may be further substituted; ring B is a 5- to 9-membered
       nitrogen-containing non-aromatic heterocyclic ring which may be further
       substituted; R.sup.1 and R.sup.2 are the same or different and are
       hydrogen atom, a hydrocarbon group which may be substituted or a
       heterocyclic group which may be substituted; or R.sup.1 and R.sup.2,
       together with the adjacent nitrogen atom, may form a nitrogen-containing
       heterocyclic ring which may be substituted; or R.sup.2, together with
       the adjacent nitrogen atom and Y, may form a nitrogen-containing
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heterocyclic ring which may be substituted; or a salt thereof is useful as a preventive or therapeutic agent for obesity, etc.

SUMM . . . now becoming a social problem. In addition, not only is obesity a serious risk factor for life-style diseases such as **diabetes**, hypertension, and arteriosclerosis; it is also widely known that increased body weight places excessive burdens on joints such as knee. . .

SUMM [0025] As specific examples thereof, there are described [7-(2-dimethylaminoethoxy)-6-methoxy-3,4-dihydro-2H-quinolin-1-yl]-[2'-**methyl**-4'-(5-**methyl**-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methanone, [7-(2-dimethylaminopropyl)-6-methoxy-3,4-dihydro-2H-quinolin-1-yl]-[2'-**methyl**-4'-(5-**methyl**-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methanone, etc.

SUMM . . . group, piperidinyl group which may have a phenyl-lower alkyl group on the piperidine ring, a carbamoyl-substituted lower alkyl group, a **pyridyl**-substituted lower alkyl group, **pyridyl** group, a group of -ANR.sup.39R.sup.40 (A is as defined above, R.sup.39 and R.sup.40 are the same or different and are. . .

SUMM . . . the above 1) in combination with at least one species selected from the group consisting of an agent for treating **diabetes**, an agent for treating hypertension and an agent for treating arteriosclerosis;

SUMM [0127] Specific examples of the "monocyclic aromatic groups" include phenyl, 2- or 3-thienyl, 2-, 3-, or 4-**pyridyl**, 2- or 3-furyl, 2-, 4- or 5-thiazolyl, 2-, 4- or 5-oxazolyl, 1-, 3- or 4-pyrazolyl, 2-pyrazinyl, 2-, 4- or 5-pyrimidinyl,. . .

SUMM . . . 2-, 3- or 4-biphenylyl; 3-(1-naphthyl)-1,2,4-oxadiazol-5-yl; 3-(2-naphthyl)-1, 2, 4-oxadiazol-5-yl; 3-(2-benzofuranyl)-1,2,4-oxadiazol-5-yl; 3-phenyl-1,2,4-oxadiazol-5-yl; 3-(2-benzoxazolyl)-1,2,4-oxadiazol-5-yl; 3-(3-indolyl)-1,2,4-oxadiazol-5-yl; 3-(2-indolyl)-1,2,4-oxadiazol-5-yl; 4-phenylthiazol-2-yl; 4-(2-benzofuranyl)thiazol-2-yl; 4-phenyl-1,3-oxazol-5-yl; 5-phenyl-isothiazol-4-yl; 5-phenyloxazol-2-yl; 4-(2-thienyl)phenyl; 4-(3-thienyl)phenyl; 3-(3-**pyridyl**)phenyl; 4-(3-**pyridyl**)phenyl; 6-phenyl-3-**pyridyl**; 5-phenyl-1,3,4-oxadiazol-2-yl; 4-(2-naphthyl)phenyl; 4-(2-benzofuranyl)phenyl; 4,4'-terphenyl; 5-phenyl-2-**pyridyl**; 2-phenyl-5-pyrimidinyl; 4-(4-**pyridyl**)phenyl; 2-phenyl-1,3-oxazol-5-yl; 2,4-diphenyl-1,3-oxazol-5-yl; 3-phenyl-isoxazol-5-yl; 5-phenyl-2-furyl; 4-(2-furyl)phenyl; etc.

SUMM . . . a C.sub.6-14 monocyclic or condensed polycyclic aromatic hydrocarbon and 5- to 10-membered aromatic heterocyclic ring (preferably, 2-, 3- or 4-biphenylyl; 6-phenyl-3-**pyridyl**, 5-phenyl-2-**pyridyl**, etc.)".

SUMM [0151] Specific examples of the above "optionally halogenated C.sub.1-6 alkyl" include C.sub.1-6 alkyl (e.g. **methyl**, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.) which may have 1 to 5, preferably 1 to 3, halogen atoms (e.g. fluorine, chlorine, bromine, iodine, etc.). Specific examples include **methyl**, chloromethyl, difluoromethyl, trichloromethyl, trifluoromethyl, ethyl, 2-bromoethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, propyl, 3,3,3-trifluoropropyl, isopropyl, butyl, 4,4,4-trifluorobutyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 5,5,5-trifluoropentyl,. . .

SUMM [0156] Examples of the "C.sub.7-19 aralkyl" in the above "C.sub.7-19 aralkyl which may be substituted" include **benzyl**, phenethyl, diphenylmethyl, triphenylmethyl, 1-naphthylmethyl, 2-naphthylmethyl, 2,2-diphenylethyl, 3-phenylpropyl, 4-phenylbutyl, 5-phenylpentyl, etc. **Benzyl** is particularly preferred.

SUMM . . . from nitrogen, sulfur and oxygen atom in addition to carbon atoms. Specific examples include 2- or 3-thienyl; 2-, 3- or 4-**pyridyl**; 2- or 3-furyl; 2-, 4- or 5-thiazolyl; 2-, 4- or 5-oxazolyl; 1-, 3- or 4-pyrazolyl; 2-pyrazinyl; 2-, 4- or

5-pyrimidinyl;. . .

SUMM [0180] a) C.sub.1-6 alkyl (e.g. **methyl**, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.);

SUMM [0185] f) C.sub.7-19 aralkyl (e.g. **benzyl**, phenethyl, diphenylmethyl, triphenylmethyl, 1-naphthylmethyl, 2-naphthylmethyl, 2,2-diphenylethyl, 3-phenylpropyl, 4-phenylbutyl, 5-phenylpentyl, etc.), preferably **benzyl**, phenethyl, 3-phenylpropyl;

SUMM . . . substituted with one to three C.sub.1-6 alkyl (e.g., phenylamino, 2,6-dimethylphenylamino, etc.), N--C.sub.1-6 alkyl-N-(C.sub.6-14 aryl optionally substituted with C.sub.1-6 alkyl)amino (e.g., N-**methyl**-N-phenylamino, N-ethyl-N-(methylphenyl)amino, etc.), 5- or 6-membered monocyclic aromatic heterocyclic ring amino optionally substituted with nitro (e.g., nitropyridylamino, etc.), 5- to 8-membered. . .

SUMM . . . atoms in addition to carbon atoms. Specific examples include aromatic heterocyclic groups such as 2- or 3-thienyl; 2-, 3- or 4-**pyridyl**; 2- or 3-furyl; 2-, 4- or 5-thiazolyl; 2-, 4- or 5-oxazolyl; 1-, 3- or 4-pyrazolyl; 2-pyrazinyl; 2-, 4- or 5-pyrimidinyl;. . .

SUMM [0207] Examples of the "C.sub.1-6 alkyl" represented by R.sup.4 include **methyl**, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.

SUMM . . . a halogen atom (preferably fluorine, chlorine and bromine, etc.); nitro; C.sub.1-3 alkylenedioxy (preferably methylenedioxy, etc.); optionally halogenated C.sub.1-6 alkyl (preferably, **methyl**, ethyl, propyl, trifluoromethyl, tert-butyl, etc.); hydroxy-C.sub.1-6 alkyl (preferably hydroxymethyl, etc.); optionally halogenated C.sub.3-6 cycloalkyl (preferably cyclohexyl, etc.); optionally halogenated C.sub.1-6. . .

SUMM . . . group which may be substituted" represented by R and Ar.sup.1 is a halogen atom (preferably chlorine, etc.), C.sub.1-6 alkyl (preferably **methyl**, etc.), C.sub.7-19 aralkyloxy which may be substituted with C.sub.1-6 alkoxy (preferably methoxybenzyloxy, etc.), etc.

SUMM [0227] R and Ar.sup.1 are preferably phenyl, biphenylyl (preferably 4-biphenylyl), phenyl-**pyridyl** (preferably 6-phenyl-3-**pyridyl**, 5-phenyl-2-**pyridyl**), phenyl-furyl (preferably 5-phenyl-2-furyl), phenyl-isoxazole (preferably 3-phenyl-isoxazol-5-yl), diphenyl-oxazole (preferably 2,4-diphenyl-1,3-oxazol-5-yl), **pyridyl**-phenyl (preferably 4-(4-**pyridyl**)phenyl), phenyl-pyrimidinyl (preferably 2-phenyl-5-pyrimidinyl), benzofuranyl-phenyl (preferably 4-(2-benzofuranyl)phenyl), furyl-phenyl (preferably 4-(2-furyl)phenyl), pyrrolyl (preferably 1-pyrrolyl) or naphthyl; each of which may have 1. . . a halogen atom (preferably fluorine, chlorine and bromine, etc.); nitro; C.sub.1-3 alkylenedioxy (preferably methylenedioxy, etc.); optionally halogenated C.sub.1-6 alkyl (preferably, **methyl**, ethyl, propyl, trifluoromethyl, tert-butyl, etc.); hydroxy-C.sub.1-6 alkyl (preferably hydroxymethyl, etc.); optionally halogenated C.sub.3-6 cycloalkyl (preferably cyclohexyl, etc.); optionally halogenated C.sub.1-6. . .

SUMM [0277] Here, examples of the "C.sub.1-6 alkyl" in the "C.sub.1-6 alkyl which may be substituted" include **methyl**, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc. Especially, **methyl**, ethyl, propyl, etc. are preferred.

SUMM . . . one to three C.sub.1-6 alkyl (e.g., phenylamino, 2,6-dimethylphenylamino, etc.), N--C.sub.1-6 alkyl-N-(C.sub.6-14 aryl which may be substituted with C.sub.1-6 alkyl)amino (e.g., N-**methyl**-N-phenylamino, N-ethyl-N-(methylphenyl)amino, etc.), 5- or 6-membered monocyclic aromatic heterocyclic ring amino which may be substituted with nitro (e.g., nitropyridylamino, etc.), 5-. . .

SUMM [0282] The "aromatic groups" are preferably phenyl, naphthyl, furyl, **pyridyl**, imidazoly, indolyl, etc. And, the "substituents" are

preferably C.sub.1-3 alkylenedioxy (e.g., methylenedioxy, etc.), optionally halogenated C.sub.1-6 alkyl (e.g., trifluoromethyl, etc.),. . .

SUMM . . . piperidinyl, etc. Further, the "substituent" in the "heterocyclic group which may be substituted" is preferably optionally halogenated C.sub.1-6 alkyl (e.g., **methyl**, etc.), C.sub.7-19 aralkyl (e.g., **benzyl**, etc.), etc. The number of the substituents is, for example, 1 to 5.

SUMM [0287] The "substituents" are preferably hydroxy; optionally halogenated C.sub.1-6 alkyl (preferably **methyl**, ethyl, etc.); C.sub.6-14 aryl (e.g., phenyl, naphthyl, etc.) which may have 1 to 3 substituents selected from halogen atom, optionally. . . halogenated C.sub.1-6 alkyl and optionally substituted C.sub.1-6 alkoxy; carbamoyl; hydroxy-C.sub.1-6 alkyl; C.sub.1-6 alkoxy-carbonyl-C.sub.1-6 alkyl (e.g., ethoxycarbonylmethyl, etc.); C.sub.7-19 aralkyl (e.g., **benzyl**, diphenylmethyl, etc.) which may be substituted with C.sub.1-3 alkylenedioxy (e.g., methylenedioxy, etc.); 5- to 10-membered aromatic heterocyclic group (preferably **pyridyl**, pyrimidinyl, etc.); 5- to 8-monocyclic non-aromatic heterocyclic group (e.g., pyrrolidinyl, piperidinyl, etc.); C.sub.8-19 aryl-alkenyl (e.g., 3-phenyl-2-prop-2-enyl, etc.); C.sub.1-6 alkyl-carboxamide (e.g.,. . .

SUMM . . . Preferably, Rb is a hydrocarbon group which may be substituted and specific examples thereof include optionally halogenated C.sub.1-6 alkyl (preferably **methyl**, ethyl, etc.); C.sub.6-14 aryl (e.g., phenyl, naphthyl, etc.) which may have 1 to 3 substituents selected from halogen atom (e.g., fluorine, chlorine, etc.), optionally halogenated C.sub.1-6 alkyl (e.g., **methyl**, etc.) and optionally substituted C.sub.1-6 alkoxy (e.g., methoxy, etc.); hydroxy-C.sub.1-6 alkyl; C.sub.1-6 alkoxy-carbonyl-C.sub.1-6 alkyl (e.g., ethoxycarbonylmethyl, etc.); C.sub.7-19 aralkyl (e.g., **benzyl**, diphenylmethyl, etc.) which may be substituted with C.sub.1-3 alkylenedioxy (e.g., methylenedioxy, etc.); C.sub.8-19 arylalkenyl (e.g., 3-phenyl-2-prop-2-enyl, etc.); 5- to 8-monocyclic. . .

SUMM [0325] 1-[[6-(4-chlorophenyl)-3-pyridinyl]carbonyl]-6-[1-**methyl**-3-piperidinylidene)**methyl**-1,2,3,4-tetrahydroquinoline;

SUMM [0330] 4-[4-(4-chlorophenyl)-1-piperidinyl]-4-oxo-1-(3-**methyl**-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-butanone;

SUMM [0333] 1-(3-**benzyl**-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-4-[4-(4-chlorophenyl)-1-piperidinyl]-4-oxo-1-butanone;

SUMM [0337] 4-[4-(4-chlorophenyl)-1-piperidinyl]-1-(2-**methyl**-2,3,4,5-tetrahydro-1H-2-benzazepin-8-yl)-4-oxo-1-butanone;

SUMM [0347] 4-[4-(4-chlorophenyl)-1-piperidinyl]-1-(3-**methyl**-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-butanone;

SUMM [0353] 7-[3-[4-(4-chlorophenyl)-1-piperidinyl]propoxy]-3-**methyl**-2,3,4,5-tetrahydro-1H-3-benzazepine;

SUMM [0356] 3-**benzyl**-7-[3-[4-(4-chlorophenyl)-1-piperidinyl]propoxy]-2,3,4,5-tetrahydro-1H-3-benzazepine;

SUMM [0393] 2-**benzyl**-8-[3-[4-(4-chlorophenyl)-1-piperidinyl]propoxy]-2,3,4,5-tetrahydro-1H-2-benzazepine;

SUMM . . . acylated, alkylated, or phosphorylated [e.g. compounds in which amino groups of compound (I') or (I") have been eicosanoylated, aranylated, pentylaminocarbonylated, (5-**methyl**-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylated, tetrahydrofuranylated, pyrrolidylmethylated, pivaloyloxymethylated, tert-butylated, etc.]; compounds in which hydroxyl groups of compound (I') or (I") have been acylated, alkylated, phosphorylated,. . . [e.g. compounds in which carboxyl groups of compound (I') or (I") have been ethylesterified, phenylesterified, carboxylmethylesterified, dimethylaminomethylesterified, pivaloyloxymethylesterified, ethoxycarbonyloxyethylesterified, phthalidylesterified, (5-**methyl**-2-oxo-1,3-dioxolen-4-yl)methylesterified, cyclohexyloxycarbonylethylesterified, or methylamidated, etc.]. These

compounds can be produced from compound (I') or (I") using per se known methods.

SUMM [0602] Examples of the protecting group for carboxy include C.sub.1-6 alkyl (e.g. **methyl**, ethyl, propyl, isopropyl, butyl, tert-butyl, etc.), C.sub.7-11 aralkyl (e.g. **benzyl**, etc.), phenyl, trityl, silyl (e.g. trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-butyldimethylsilyl, tert-butyldiethylsilyl, etc.), C.sub.2-6 alkenyl (e.g. 1-allyl, etc.). These groups may be. . .

SUMM [0603] Examples of the protective group for hydroxy include C.sub.1-6 alkyl (e.g. **methyl**, ethyl, propyl, isopropyl, butyl, tert-butyl, etc.), phenyl, trityl, C.sub.7-10 aralkyl (e.g. **benzyl**, etc.), formyl, C.sub.1-6 alkyl-carbonyl (e.g. acetyl, propionyl, etc.), benzoyl, C.sub.7-10 aralkyl-carbonyl (e.g. benzylcarbonyl, etc.), 2-tetrahydropyranyl, 2-tetrahydrofuranyl, silyl (e.g. trimethylsilyl, triethylsilyl,. . . groups may be substituted by 1 to 3 of halogen atom (e.g. fluorine, chlorine, bromine, iodine, etc.), C.sub.1-6 alkyl (e.g. **methyl**, ethyl, n-propyl, etc.), C.sub.1-6 alkoxy (e.g. methoxy, ethoxy, propoxy, etc.) or nitro, etc.

SUMM . . . The compound of the present invention is also useful as an agent for preventing or treating lifestyle diseases such as **diabetes**, diabetic complications (e.g. diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, etc.), arteriosclerosis, gonitis, etc.

SUMM . . . the pharmaceutical composition of the present invention can be used in combination with an alimentary therapy (e.g., alimentary therapy for **diabetes**) and exercise.

SUMM [0620] Examples of the solubilizing agents include polyethylene glycol, propylene glycol, D-mannitol, **benzyl** benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate, etc.

SUMM [0624] Examples of the soothing agents include **benzyl** alcohol, etc.

SUMM [0625] Examples of the antiseptics include paraoxybenzoates, chlorobutanol, **benzyl** alcohol, phenethylalcohol, dehydroacetic acid, sorbic acid, etc.

SUMM . . . effect against obesity", "reduction of dose of MCH antagonist", etc. Examples of the concomitant drugs include a "agents for treating **diabetes**", "agents for treating diabetic complications", "agents for treating obesity other than MCH antagonists", "agents for treating hypertension", "agents for treating. . .

SUMM [0632] Examples of the above "agents for treating **diabetes**" include insulin sensitizers, insulin secretion enhancers, biguamides, insulins, .alpha.-glucosidase inhibitors, 3 adrenaline receptor agonists, etc.

SUMM . . . enhancers include sulfonylureas. Specific examples of the sulfonylureas include tolbutamide, chlorpropamide, tolazamide, acetohexamide, glyclopyramide and its ammonium salt, glibenclamide, gliclazide, **glimepiride**, etc.

SUMM [0641] Other than the above, examples of the "agents for treating **diabetes**" include ergoset, pramlintide, leptin, BAY-27-9955, etc.

SUMM . . . WSC 1-ethyl-3-(3-dimethylaminopropyl) carbodimide hydrochloride

.sup.1H-NMR proton nuclear resonance (Free substances were usually measured in CDCl.sub.3.)

IR infrared absorption spectrum

Me **methyl**

Et ethyl

HOBt 1-hydroxy-1H-benzotriazole

IPE diisopropyl ether

DMAP 4-dimethylaminopyridine

SUMM . . . lysine

Arg	arginine
His	histidine
Phe	phenylalanine
Tyr	tyrosine
Tro	tryptophan
Pro	proline
Asn	asparagine
Gln	glutamine
pGl	pyroglutamine
Me	**methyl** group
Et	ethyl group
Bu	butyl group
Ph	phenyl group
TC	**thiazolidine**-4(R)-carboxamide group

SUMM . . . and reagents frequently used in this specification, are shown by the following symbols.

Tos	p-toluenesulfonyl
CHO	formyl
Bzl	**benzyl**
Cl.sub.2Bzl	2,6-dichlorobenzyl
Bom	benzyloxymethyl
Z	benxyloxycarbonyl
Cl-Z	2-chlorobenzyloxycarbonyl
Br-Z	2-bromobenzyloxycarbonyl
Boc	t-butoxycarbonyl
DNP	dinitrophenol
Trt	trityl
Bum	t-butoxymethyl
Fmoc	N-9-fluorenylmethoxycarbonyl

. . .

DETD . . . mL) and then added to a suspension of 6-acetyl-1,2,3,4-tetrahydroquinoline (0.7 g), sodium hydroxide powder (0.31 g) and tetrabutyl ammonium hydrogensulfate (**12 mg**) in tetrahydrofuran (15 mL). After the mixture was stirred at room temperature for 3 hours, water was added to the. . .

DETD [0771] **Methyl** 3-(4-ethoxycarbonylmethoxy-3-nitrophenyl)propionate ##STR63##

DETD . . . ethyl acetate. The extract was washed with water and aqueous saturated sodium bicarbonate, dried over magnesium sulfate and concentrated, whereby **methyl** 3-(4-hydroxy-3-nitrophenyl)propionate (47 g) was obtained as powder.

DETD [0778] 3) Using **methyl** 3-(4-hydroxy-3-nitrophenyl)propionate obtained in 2) above, the title compound was obtained as powder by the same procedure as in 3) in. . .

DETD [0781] 1) Using **methyl** 3-(4-ethoxycarbonylmethoxy-3-nitrophenyl)propionate obtained in Reference Example 18, **methyl** 3-(3,4-dihydro-2H-1,4-benzoxazine-3-oxo-6-yl)propionate was obtained as powder by the same procedure as in Example 133.

DETD [0784] 2) 1 N borane/THF solution (150 ml, 150 mmol) was added to a solution of **methyl** 3-(3,4-dihydro-2H-1,4-benzoxazine-3-oxo-6-yl)propionate (24 g, 102 mmol) obtained in 1) above in THF (400 ml) under cooling with ice-bath. The reaction solution. . .

DETD [0910] 4-[4-(4-Chlorophenyl)-1-piperidinyl]-4-oxo-1-(3-**methyl**-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-butanone ##STR89##

DETD [0925] 1-(3-**Benzyl**-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-4-[4-(4-chlorophenyl)-1-piperidinyl]-4-oxo-1-butanone ##STR92##

DETD [0999] 4-[4-(4-Chlorophenyl)-1-piperidinyl]-1-(3-**methyl**-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-butanone ##STR108##

DETD N-**Benzyl**-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-

yl)butanamide Trifluoroacetate

DETD [1054] 4-Oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-N-[4-(trifluoromethyl)**benzyl**]butanamide Trifluoroacetate ##STR125##

DETD [1078] N-**Methyl**-N-(1-naphthylmethyl)-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide Trifluoroacetate ##STR133##

DETD [1081] N-[2-(3,4-Dimethoxyphenyl)ethyl]-N-**methyl**-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide Trifluoroacetate ##STR134##

DETD [1111] N-Cyclohexyl-N-**methyl**-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide Trifluoroacetate ##STR144##

DETD [1114] N-**Benzyl**-N-**methyl**-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide Trifluoroacetate ##STR145##

DETD [1132] 4-((2S)-2-[[(2,6-Dimethylphenyl)amino]**methyl**]pyrrolidin-1-yl)-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butan-1-one Trifluoroacetate ##STR151##

DETD [1156] N-[3-[**Methyl**(phenyl)amino]propyl]-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide Trifluoroacetate ##STR159##

DETD [1213] N-[2-(Dimethylamino)ethyl]-N-**methyl**-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanehydrazide Trifluoroacetate ##STR178##

DETD [1216] N-(1-Benzylpyrrolidin-3-yl)-N-**methyl**-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide Trifluoroacetate ##STR179##

DETD [1252] N-**Benzyl**-N-(1-benzylpyrrolidin-3-yl)-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide Trifluoroacetate ##STR191##

DETD [1258] 4-(4-**Methyl**-1,4-diazepin-1-yl)-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butan-1-one Trifluoroacetate ##STR193##

DETD [1273] N-**Benzyl**-N-[2-(dimethylamino)ethyl]-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide Trifluoroacetate ##STR198##

DETD [1276] N-**Methyl**-N-(1-methylpiperazin-4-yl)-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide Trifluoroacetate ##STR199##

DETD [1285] N-**Benzyl**-N-(2-carboxyethyl)-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide Trifluoroacetate ##STR202##

DETD [1294] 4-[4-(4-Chlorophenyl)-1-piperidinyl]-1-(2-**methyl**-2,3,4,5-tetrahydro-1H-2-benzazepin-8-yl)-4-oxo-1-butanone ##STR204##

DETD [1409] 1-(2-**Benzyl**-2,3,4,5-tetrahydro-1H-2-benzazepin-8-yl)-4-[4-(4-chlorophenyl)piperidin-1-yl]-4-oxobutan-1-one Hydrochloride ##STR232##

DETD [1415] 4-[4-(4-Chlorophenyl)piperidin-1-yl]-1-(2-**methyl**-2,3-dihydro-1H-isoindol-5-yl)-4-oxobutan-1-one ##STR234##

DETD [1424] 1-(2-**Benzyl**-2,3-dihydro-1H-isoindol-5-yl)-4-[4-(4-chlorophenyl)piperidin-1-yl]-4-oxobutan-1-one ##STR237##

DETD [1430] N-(1-**Methyl**-3-phenylpropyl)-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-butanamide Hydrochloride ##STR239##

DETD [1433] 4-(3-Isopropyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-N-(1-**methyl**-3-phenylpropyl)-4-oxobutanamide Hydrochloride ##STR240##

DETD [1434] Using N-(1-**methyl**-3-phenylpropyl)-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-butanamide hydrochloride obtained in Example 166, the title compound was obtained as amorphous powder by the same procedure as in Example. . .

DETD [1519] 4-[4-(4-Chlorophenyl)-1-piperidinyl]1-1(2-**methyl**-1,2,3,4-tetrahydro-7-isoquinolinyl)-4-oxo-1-butanone ##STR262##

DETD [1527] 1-(2-**Benzyl**-1,2,3,4-tetrahydro-7-isoquinolinyl)-4-[4-(4-chlorophenyl)-1-piperidinyl]-4-oxo-1-butanone ##STR264##

DETD [1555] 4-[4-(4-Methylphenyl)-1-piperidinyl]-1-(3-**methyl**-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-4-oxo-1-butanone ##STR271##

DETD [1567] 4-[4-(4-Methylphenyl)-1-piperidinyl]-1-(2-**methyl**-1,2,3,4-tetrahydro-7-isoquinolinyl)-4-oxo-1-butanone ##STR274##

DETD [1575] 1-(2-**Benzyl**-1,2,3,4-tetrahydro-7-isoquinolinyl)-4-[4-(4-

methylphenyl)-1-piperidinyl]-4-oxo-1-butanone Hydrochloride ##STR276##
DETD [1594] 8-[3-[4-(4-Chlorophenyl)-1-piperidinyl]propoxy]-2-**methyl**-2,3,4,5-tetrahydro-1H-2-benzazepine Hydrochloride ##STR281##
DETD [1604] 1-(3-**Benzyl**-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-4-[4-(4-chlorophenyl)-1-piperidinyl]-1-butanone ##STR284##
DETD [1628] N-[3-(4-Chlorophenyl)propyl]-N-**methyl**-4-oxo-4-[3-(trifluoroacetyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]butanamide ##STR291##
DETD [1631] N-[3-(4-Chlorophenyl)propyl]-N-**methyl**-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide Hydrochloride ##STR292##
DETD [1632] Using N-[3-(4-chlorophenyl) propyl]-N-**methyl**-4-oxo-4-[3-(trifluoroacetyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]butanamide obtained in Example 218, the title compound was obtained as amorphous powder by the same procedure as in Example 13.
CLM What is claimed is:
. . . to claim 1 in combination with at least one species selected from the group consisting of an agent for treating **diabetes**, an agent for treating hypertension and an agent for treating arteriosclerosis.

L3 ANSWER 2 OF 15 USPATFULL on STN
AN 2003:201447 USPATFULL
TI Combinations comprising dipeptidylpeptidase-iv inhibitor
IN Balkan, Bork, Madison, CT, UNITED STATES
Hughes, Thomas Edward, Somerville, NJ, UNITED STATES
Holmes, David Grenville, Binningen, SWITZERLAND
Villhauer, Edwin Bernard, Morristown, NJ, UNITED STATES
PI US 2003139434 A1 20030724
AI US 2002-181169 A1 20021010 (10)
WO 2001-EP590 20010119
PRAI US 2000-9489234 20000121
US 2000-9619262 20000719
DT Utility
FS APPLICATION
LREP THOMAS HOXIE, NOVARTIS, PATENT AND TRADEMARK DEPARTMENT, ONE HEALTH PLAZA 430/2, EAST HANOVER, NJ, 07936-1080
CLMN Number of Claims: 16
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1581
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to a combination which comprises a DPP-IV inhibitor and at least one further antidiabetic compound, preferably selected from the group consisting of insulin signalling pathway modulators, like inhibitors of protein tyrosine phosphatases (PTPases), non-small molecule mimetic compounds and inhibitors of glutamine-fructose-6-phosphate amidotransferase (GFAT), compounds influencing a dysregulated hepatic glucose production, like inhibitors of glucose-6-phosphatase (G6Pase), inhibitors of fructose-1,6-bisphosphatase (F-1,6-BPase), inhibitors of glycogen phosphorylase (GP), glucagon receptor antagonists and inhibitors of phosphoenolpyruvate carboxykinase (PEPCK), pyruvate dehydrogenase kinase (PDHK) inhibitors, insulin sensitivity enhancers, insulin secretion enhancers, .alpha.-glucosidase inhibitors, inhibitors of gastric emptying, insulin, and .alpha..sub.2-adrenergic antagonists, for simultaneous, separate or sequential use in the prevention, delay of progression or treatment of conditions mediated by dipeptidylpeptidase-IV (DPP-IV), in particular **diabetes**, more especially type 2 **diabetes** mellitus, conditions of impaired glucose tolerance (IGT), conditions of impaired fasting plasma glucose, metabolic acidosis, ketosis, arthritis, obesity and osteoporosis; and the use of such combination for the cosmetic

treatment of a mammal in order to effect a cosmetically beneficial loss of body weight.

AB . . . separate or sequential use in the prevention, delay of progression or treatment of conditions mediated by dipeptidylpeptidase-IV (DPP-IV), in particular **diabetes**, more especially type 2 **diabetes** mellitus, conditions of impaired glucose tolerance (IGT), conditions of impaired fasting plasma glucose, metabolic acidosis, ketosis, arthritis, obesity and osteoporosis;. . .

SUMM . . . or sequential use, especially in the prevention, delay of progression or treatment of conditions mediated by dipeptidylpeptidase-IV (DPP-IV), in particular **diabetes**, more particular type 2 **diabetes** mellitus, conditions of impaired glucose tolerance (IGT), conditions of impaired fasting plasma glucose, metabolic acidosis, ketosis, arthritis, obesity and osteoporosis;. . .

SUMM [0003] Non-insulin dependent **diabetes** mellitus (type 2 **diabetes** mellitus) is characterized by both increased peripheral insulin resistance and abnormal insulin secretion. At least three abnormalities of insulin secretion. . . levels. Several metabolic, hormonal, and pharmacological entities are known to stimulate insulin secretion including glucose, amino-acids and gastrointestinal peptides. The **Diabetes** Control and Complications Trial (DCCT) has established that lowering of blood glucose is associated with decreases in the onset and progression of diabetic microvascular complications (**Diabetes** Control and Complications Trial Research Group; N. Engl. J. Med. 1993, 329, 977-986). IGT is an impairment of glucose homeostasis closely related to type 2 **diabetes** mellitus. Both conditions convey a great risk of macrovascular disease. Therefore, one therapeutic focus is on optimizing and potentially normalizing glycemic control in subjects with type 2 **diabetes** mellitus, conditions of impaired fasting plasma glucose, or IGT. Presently available agents need to be improved in order to better. . .

SUMM . . . of impaired glucose tolerance (IGT), conditions of impaired fasting plasma glucose, metabolic acidosis, ketosis, arthritis, obesity and osteoporosis, and preferably **diabetes**, especially type 2 **diabetes** mellitus. Such a combination is preferably a combined preparation or a pharmaceutical composition.

SUMM [0009] Lower alkyl is, if not stated otherwise, preferably ethyl or, most preferably, **methyl**. (C.sub.1-8)Alkyl is branched or preferably unbranched alkyl, preferably lower alkyl, e.g. **methyl** or ethyl.

SUMM . . . which is unsubstituted or substituted by one or two lower alkyl groups is, for example, pyrrolidinyl, methylpyrrolidinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 2-**methyl**-1-piperidinyl or hexamethylenimino. Preferably, C.sub.4-C6-alkylenimino is 1-piperidinyl.

SUMM [0015] A [3.1.1]bicyclic carbocyclic moiety optionally substituted as defined above preferably is bicyclo[3.1.1]hept-2-yl optionally disubstituted in 6-position with **methyl**, or bicyclo[3.1.1]-hept-3-yl optionally trisubstituted with one **methyl** in 2-position and two **methyl** groups in 6-position. A [2.2.1]bicyclic carbocyclic moiety optionally substituted as defined above preferably is bicyclo[2.2.1]hept-2-yl.

SUMM . . . imidazolyl, imidazolinyl, imidazolidinyl, oxazolyl, oxazolidinyl, isoxazolinyl, isoxazolyl, thiazolyl, thiadiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, furyl, tetrahydrofuryl, thienyl, oxadiazolyl, piperidinyl, piperazinyl, azepinyl, 4-piperidinyl, **pyridyl**, pyrazinyl, pyrimidinyl, pyridazinyl, tetrahydropyranyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 1,3-dioxolane, indolyl, benzothiazolyl, benzoxazolyl, benzothienyl, quinuclidinyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl,. . .

SUMM [0033] g) R.sub.5 wherein R.sub.5 is: indanyl; a pyrrolidinyl or piperidinyl moiety optionally substituted with **benzyl**; a

[2.2.1]- or [3.1.1]bicyclic carbocyclic moiety optionally mono- or plurisubstituted with (C.sub.1-8)alkyl; adamantyl; or (C.sub.1-8)alkyl optionally mono- or independently plurisubstituted. . .

SUMM . . . 98/19998 and Example 1 of WO 00/34241, respectively. A DPP-IV inhibitor of formula VI (see above) is specifically described in **Diabetes** 1998, 47, 1253-1258. DPP728 can be formulated as described on page 20 of WO 98/19998.

SUMM . . . inhibiting the activity of G6Pase. Examples of such compounds are disclosed in WO 00/14090, WO 99/40062, WO 98/40385, EP682024 and **Diabetes** 1998, 47,1630-1636.

SUMM . . . or inhibiting the activity of PEPCK. Examples of such compounds are disclosed in U.S. Pat. No. 6,030,837 and Mol. Biol. **Diabetes** 1994,2, 283-99.

SUMM [0095] The antidiabetic thiazolidinedione (glitazone) is, for example, (S)-((3,4-dihydro-2-(phenyl-**methyl**)-2H-1-benzopyran-6-yl) **methyl**-**thiazolidine**-2,4-dione (englitazone), 5-{[4-(3-(5-**methyl**-2-phenyl-4-oxazolyl)-1-oxopropyl)-phenyl]-**methyl**}-**thiazolidine**-2,4-dione (darglitazone), 5-{[4-(1-**methyl**-cyclohexyl)methoxy)-phenyl]**methyl**]-**thiazolidine**-2,4-dione (ciglitazone), 5-{[4-(2-(1-indolyl)ethoxy)phenyl]**methyl**}-**thiazolidine**-2,4-dione (DRF2189), 5-{4-[2-(5-**methyl**-2-phenyl-4-oxazoly)-ethoxy)] **benzyl**}-**thiazolidine**-2,4-dione (BM-13.1246), 5-(2-naphthylsulfonyl)-**thiazolidine**-2,4-dione (AY-31637), bis{4-[(2,4-dioxo-5-thiazolidinyl)-**methyl**]phenyl}methane (YM268), 5-{4-[2-(5-**methyl**-2-phenyl-4-oxazolyl)-2-hydroxyethoxy]-**benzyl**}-**thiazolidine**-2,4-dione (AD-5075), 5-[4-(1-phenyl-1-cyclopropanecarbonylamino)-**benzyl**]-**thiazolidine**-2,4-dione (DN-108) 5-{[4-(2-(2,3-dihydroindol-1-yl)ethoxy)phenylmethyl)-**thiazolidine**-2,4-dione, 5-[3-(4-chloro-phenyl])-2-propynyl]-5-phenylsulfonyl) **thiazolidine**-2,4-dione, 5-[3-(4-chlorophenyl])-2-propynyl]-5-(4-fluorophenyl-sulfonyl)**thiazolidine**-2,4-dione,5-{[4-(2-(**methyl**-2-pyridinyl-amino)-ethoxy)phenyl]**methyl**}-**thiazolidine**-2,4-dione (rosiglitazone), 5-{[4-(2-(5-ethyl-2-**pyridyl**)ethoxy)phenyl]-**methyl**}-**thiazolidine** -2,4-dione (pioglitazone), 5-{[4-((3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy)-phenyl]-**methyl**)-**thiazolidine**-2,4-dione (troglitazone), 5-[6-(2-fluoro-benzyloxy)-naphthalen-2-ylmethyl]-**thiazolidine**-2,4-dione (MCC555), 5-([2-(2-naphthyl)-benzoxazol-5-yl]-**methyl**} **thiazolidine**-2,4-dione (T-174) and 5-(2,4-dioxothiazolidin-5-ylmethyl)-2-methoxy-N-(4-trifluoromethyl-**benzyl**)benzamide (KRP297).

SUMM [0107] b) **pyridyl**, lower alkyl-**pyridyl**, N-lower alkyl-N-pyridylamino or halogenphenyl,

SUMM [0115] Preferably, the compound of formula VIII is selected from the group consisting of (S)-((3,4-dihydro-2-(phenyl-**methyl**)-2H-1-benzopyran-6-yl)**methyl**-**thiazolidine**-2,4-dione (englitazone), 5-{[4-(3-(5-**methyl**-2-phenyl-4-oxazolyl)-1-oxopropyl)-phenyl]-**methyl**)-**thiazolidine**-2,4-dione (darglitazone), 5-{[4-(1-**methyl**-cyclohexyl)methoxy)-phenyl] **methyl**}-**thiazolidine**-2,4-dione (ciglitazone), 5-{[4-(2-(1-indolyl)ethoxy)phenyl]**methyl**)-**thiazolidine** -2,4-dione (DRF2189), 5-{4-[2-(5-**methyl**-2-phenyl-4-oxazoly)-ethoxy)]**benzyl**}-**thiazolidine**-2,4-dione (BM-13.1246), 5-(2-naphthylsulfonyl)-**thiazolidine**-2,4-dione (AY-31637), bis{4-[(2,4-dioxo-5-thiazolidinyl)**methyl**]phenyl}methane (YM268), 5-{4-[2-(5-**methyl**-2-phenyl-4-oxazolyl)-2-hydroxyethoxy]**benzyl**}-**thiazolidine**-2,4-dione (AD-5075), 5-[4-(1-phenyl-1-cyclopropanecarbonylamino)-**benzyl**]-**thiazolidine**-2,4-dione (DN-108) 5-{[4-(2-(2,3-dihydroindol-1-

yl)ethoxy)phenyl]**methyl**)-**thiazolidine**-2,4-dione, 5-[3-(4-chloro-phenyl])-2-propynyl]-5-phenylsulfonyl) **thiazolidine**-2,4-dione, 5-[3-(4-chlorophenyl)]-2-propynyl]-5-(4-fluorophenyl-sulfonyl)**thiazolidine**-2,4-dione, 5-[6-(2-fluoro-benzyloxy)naphthalen-2-ylmethyl]-**thiazolidine**-2,4-dione (MCC555), 5-{[2-(2-naphthyl)-benzoxazol-5-yl]-**methyl**)**thiazolidine**-2,4-dione (T-174) and 5-(2,4-dioxothiazolidin-5-ylmethyl)-2-methoxy-N-(4-trifluoromethyl-**benzyl**)benzamide (KRP297) or a pharmaceutically acceptable salt thereof.

SUMM [0116] More preferably, the compound of formula VIII is selected from the group consisting of 5-{[4-(2-(**methyl**-2-pyridinyl-amino)-ethoxy)phenyl]**methyl**}-thiazodine-2,4-dione (rosiglitazone), 5-{[4-(2-(5-ethyl-2-**pyridyl**)ethoxy)phenyl]-**methyl**}**thiazolidine**-2,4-dione (pioglitazone) and 5-{[4-((3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy)-phenyl]-**methyl**)-**thiazolidine**-2,4-dione (troglitazone), MCC555, T-1 74 and KRP297, especially rosiglitazone, pioglitazone and troglitazone, or a pharmaceutically acceptable salt thereof.

SUMM [0117] The glitazones 5-{[4-(2-(5-ethyl-2-**pyridyl**)ethoxy)phenyl]-**methyl**}**thiazolidine**-2,4-dione (pioglitazone, EP 0 193 256 A1), 5-{[4-(2-(**methyl**-2-pyridinyl-amino)-ethoxy)phenyl]**methyl**}-**thiazolidine**-2,4-dione (rosiglitazone, EP 0 306 228 A1), 5-([4-((3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy)-phenyl]-**methyl**)**thiazolidine**-2,4-dione (troglitazone, EP 0 139 421), (S)-((3,4-dihydro-2-(phenyl-**methyl**)-2H-1-benzopyran-6-yl)**methyl**-**thiazolidine**-2,4-dione (englitazone, EP 0 207 605 B1), 5-(2,4-dioxothiazolidin-5-ylmethyl)-2-methoxy-N-(4-trifluoromethyl-**benzyl**)benzamide (KRP297, JP 10087641-A), 5-[6-(2-fluoro-benzyloxy)naphthalen-2-ylmethyl]**thiazolidine**-2,4-dione (MCC555, EP 0 604 983 B1), 5-([4-(3-(5-**methyl**-2-phenyl-4-oxazolyl)-1-oxopropyl)-phenyl]-**methyl**)-**thiazolidine**-2,4-dione (darglitazone, EP 0 332 332), 5-(2-naphthylsulfonyl)-**thiazolidine**-2,4-dione (AY-31637, U.S. Pat. No. 4,997,948), 5-([4-(1-**methyl**-cyclohexyl)methoxy)-phenyl]**methyl**}-**thiazolidine**-2,4-dione (ciglitazone, U.S. Pat. No. 4,287,200) are in each case generically and specifically disclosed in the documents cited in brackets beyond. . . the claims are hereby incorporated into the present application by reference to these publications. The preparation of DRF2189 and of 5-{[4-(2-(2,3-dihydroindol-1-yl)ethoxy)phenyl]**methyl**}-**thiazolidine**-2,4-dione is described in B. B. Lohray et al., J. Med. Chem. 1998, 41,1619-1630; Examples 2d and 3g on pages 1627 and 1628. The preparation of 5-[3-(4-chlorophenyl])-2-propynyl]-5-phenylsulfonyl)-**thiazolidine**-2,4-dione and the other compounds in which A is phenylethynyl mentioned herein can be carried out according to the methods described. . .

SUMM . . . 6, or analogous to Examples 27 or 28 on page 24 of EP 0 207 605 B1; and darglitazone and 5-(4-[2-(5-**methyl**-2-phenyl-4-oxazolyl)-ethoxy)]**benzyl**)-**thiazolidine**-2,4-dione (BM-1 3.1246) can be formulated as disclosed on page 8, line 42 to line 54 of EP 0 332 332. . .

SUMM . . . and analogs thereof, very especially the compound DRF-554158, described in WO 99/08501 and the compound NC-2100 described by Fukui in **Diabetes** 2000, 49(5), 759-767.

SUMM . . . is, for example, glisoxepid, glyburide, glibenclamide, acetohexamide, chloropropamide, glibornuride, tolbutamide, tolazamide, glipizide, carbutamide, gliquidone, glyhexamide, phenbutamide or tolcyclamide; and preferably **glimepiride** or gliclazide. Tolbutamide, glibenclamide, gliclazide, glibornuride, gliquidone, glisoxepid and **glimepiride** can be administered e.g. in the form as they are marketed under the trademarks RASTINON HOECHST.TM.,

AZUGLUCON.TM., DIAMICRONT.TM., GLUBORID.TM., GLURENORM.TM.,. . .

SUMM [0130] R.delta..sub.2 is hydrogen, halogen, **methyl** or methoxy;

SUMM [0131] R.delta..sub.3 is hydrogen, C.sub.1-C.sub.7alkyl, or phenyl which is unsubstituted or substituted by halogen, **methyl** or methoxy;

SUMM [0133] W is **methyl**, hydroxymethyl, formyl, carboxy; or alkoxycarbonyl which comprises between 2 and up to and including 5 carbon atoms and in which. . .

SUMM [0142] If R.gamma..sub.2 represents heteroaryl, R.gamma..sub.2 is preferably quinolynyl, **pyridyl** or 2-benzofuranyl.

SUMM [0144] Nateglinide (N-[(trans4-isopropylcyclohexyl)-carbonyl]-D-phenylalanine, EP 196222 and EP 526171) and repaglinide ((S)-2-ethoxy-4-{2-[[3-**methyl**-1-[2-(1-piperidinyl)phenyl]butyl]-amino]-2-oxoethyl}benzoic acid, EP 0 147 850 A2, in particular Example 11 on page 61, and EP 0 207 331 A1) are. . .

SUMM . . . include, but are not limited to those disclosed in J. Clin. Endocrinol. Metab. 2000, 85(3), 1043-1048, especially CCK-8, and in **Diabetes** Care 1998; 21; 897-893, especially Amylin and analogs thereof, e.g. Pramlintide. Amylin is also described e.g. by O. G. Kolterman. . .

SUMM [0148] Examples of ".alpha..sub.2-adrenergic antagonists" include, but are not limited to midaglizole described in **Diabetes** 36,1987, 216-220.

SUMM . . . nateglinide, repaglinide, metformin, rosiglitazone, pioglitazone, troglitazone, glisoxepid, glyburide, glibenclamide, acetohexamide, chloropropamide, glibornuride, tolbutamide, tolazamide, glipizide, carbutamide, gliquidone, glyhexamide, phenbutamide, tolcyclamide, **glimepiride** and gliclazide, or the pharmaceutically acceptable salt of such a compound.

SUMM . . . Moreover, the term "prevention" means prophylactic administration of such combination to patients being in a pre-stage of the conditions, especially **diabetes**, to be treated.

SUMM . . . the combination, such as a combined preparation or pharmaceutical composition, to patients being in a pre-stage of the condition, especially **diabetes**, to be treated in which patients a pre-form of the corresponding condition is diagnosed.

SUMM [0158] The nature of conditions mediated by DPP-IV, especially **diabetes**, conditions of impaired fasting plasma glucose, and IGT, is multifactorial. Under certain circumstances, drugs with different mechanisms of action may. . .

SUMM . . . surprising prolongation of efficacy, a broader variety of therapeutic treatment and surprising beneficial effects on diseases and conditions associated with **diabetes**, e.g. less gain of weight.

SUMM . . . PARTNER OF THE INVENTION results in a more effective prevention or preferably treatment of conditions mediated by DPP-IV, in particular **diabetes**, especially type 2 **diabetes** mellitus, conditions of impaired fasting plasma glucose, and conditions of IGT.

SUMM [0165] Clinical Double-blind, Randomized, Parallel-group Study in Subjects With Type 2 **Diabetes** Mellitus Inadequately Controlled on Diet Alone

SUMM . . . the claimed combined preparation or pharmaceutical composition, respectively. The beneficial effects on conditions mediated by DPP-IV, in particular type 2 **diabetes** mellitus can be determined directly through the results of this study or by changes in the study design which are. . .

SUMM [0168] Subjects with a diagnosis of type 2 **diabetes** mellitus who have not achieved near normoglycemia (HbA.sub.1c<6.8%) on diet only are chosen for this trial. The effects on glycemic. . . same diet as in the period before treatment. Measures of glycemic control are validated surrogate endpoints for the treatment of **diabetes**. HbA.sub.1c is the single most reliable measurement for assessing glycemic control (D. Goldstein et al, Tests of Glycemia in **Diabetes**; **Diabetes** Care 1995, 18(6), 896-909) and is

the primary response variable in this study. Since glycosylation of hemoglobin is determined by. . .

SUMM . . . a different subject population can be involved in such a clinical trial, e.g. subjects with a diagnosis of type 2 **diabetes** mellitus who have achieved near normoglycemia (HbA.sub.1c<6.8%) on diet alone, subjects with diseases other than **diabetes** mellitus, e.g. other metabolic disorders, or subjects selected by other criteria, such as age or sex; the subject number can. . .

SUMM . . . invention can be used for the prevention and preferably the treatment of conditions mediated by DPP-IV, in particular type 2 **diabetes** mellitus. The combination of the present invention can also be used for the prevention and preferably the treatment of other. . .

SUMM [0186] The condition mediated by DPP-IV is preferably selected from the group consisting of **diabetes**, impaired fasting plasma glucose, impaired glucose tolerance, metabolic acidosis, ketosis, arthritis, obesity and osteoporosis.

SUMM [0187] Very preferably, the condition mediated by DPP-IV is type 2 **diabetes** mellitus.

SUMM . . . to provide a pharmaceutical composition comprising a quantity, which is jointly therapeutically effective against conditions mediated by DPP-IV, in particular **diabetes**, more especially type 2 **diabetes** mellitus, conditions of impaired fasting plasma glucose, and conditions of IGT, of a DPP-IV inhibitor (i) or a pharmaceutically acceptable. . .

SUMM . . . thereof for the preparation of a pharmaceutical preparation for the prevention or treatment of conditions mediated by DPP-IV, in particular **diabetes**, more especially type 2 **diabetes** mellitus, conditions of impaired fasting plasma glucose, and conditions of IGT.

SUMM . . . PARTNER OF THE INVENTION together with instructions for use thereof in the treatment of conditions mediated by DPP-IV, in particular **diabetes**, more especially type 2 **diabetes** mellitus, conditions of impaired fasting plasma glucose, and conditions of IGT.

SUMM . . . further aspect of the present invention is a method of treating a condition mediated by DPP-IV, in particular type 2 **diabetes** mellitus, comprising administering to a warm-blooded animal in need thereof jointly therapeutically effective amounts of a DPP-IV inhibitor in free. . .

SUMM . . . which comprises orally administering to said mammal, including man, especially man suffering from a metabolic disorder, in particular type 2 **diabetes**, a combined preparation or pharmaceutical composition described herein in a dosage effective to influence, e.g., to increase or decrease, the. . . especially a human being. Overweight is one of the risk factors for developing a metabolic disorder, in particular type 2 **diabetes**, and at the same time often the result of such a metabolic disorder, especially type 2 **diabetes**. Furthermore, a number of antidiabetics are known to cause weight gain. Hence, humans suffering from metabolic disorders, especially type 2 **diabetes**, are often faced with overweight. Therefore, the cosmetically beneficial loss of body weight can be effected especially in humans suffering from a metabolic disorder, such as type 2 **diabetes**. The combinations described herein can also be used to replace or complement an antidiabetic drug taken by a human suffering from type 2 **diabetes** in order to prevent, for cosmetic reasons, a further increase of the body weight.

SUMM . . . mg/day

glibornuride	about 5 to 150 mg/day	about 12.5 to 75 mg/day
gliclazide	about 20 to 480 mg/day	about 80 to 240 mg/day

glimepiride	about 0.25 to **12 mg** /day	about 1 to 6 mg/day
gliquidone	about 5 to 250 mg/day	about 30 to 120 mg/day
glisoxepid	about 0.5 to 25 mg/day. . .	1000 for example 100, 200, 400, 600 or 800, mg/day, mg/day
5-[3-(4-chlorophenyl])-2-propynyl]-5-phenylsulfonyl)-**thiazolidine**-2,4-dione	about 0.1 to 2500 mg/day	about 1 to 1000 mg/day
5-[3-(4-chlorophenyl])-2-propynyl]-5-(4-fluoro-phenylsulfonyl)**thiazolidine**-2,4-dione	about 0.1 to 2500 mg/day	about 1 to 1000 mg/day
N-(N'-substituted glycyl)-2-cyanopyrrolidine of formula I	about 0.1 to 250 mg/kg body weight of the patient. . .	about 1 to 100 mg/kg body

CLM What is claimed is:

. . . optionally monosubstituted in 1-position with (C.sub.1-3)hydroxyalkyl; g) R.sub.5 wherein R.sub.5 is: indanyl; a pyrrolidinyl or piperidinyl moiety optionally substituted with **benzyl**; a [2.2.1]- or [3.1.1]bicyclic carbocyclic moiety optionally mono- or plurisubstituted with (C.sub.1-8)alkyl; adamantyl; or (C.sub.1-8)alkyl optionally mono- or independently plurisubstituted. . .

. . . nateglinide, repaglinide, metformin, rosiglitazone, pioglitazone, troglitazone, glisoxepid, glyburide, glibenclamide, acetohexamide, chloropropamide, glibornuride, tolbutamide, tolazamide, glipizide, carbutamide, gliquidone, glyhexamide, phenbutamide, tolcyclamide, **glimepiride** and gliclazide, or the pharmaceutically acceptable salt of such a compound.

L3 ANSWER 3 OF 15 USPATFULL on STN
AN 2003:159946 USPATFULL
TI Treatment of **diabetes** with thiazolidinedione and sulphonylurea
IN Buckingham, Robin Edwin, Hertfordshire, UNITED KINGDOM
Smith, Stephen Alistair, Hertfordshire, UNITED KINGDOM
PA SmithKline Beecham p.l.c. (non-U.S. corporation)
PI US 2003109561 A1 20030612
AI US 2003-346947 A1 20030117 (10)
RLI Continuation of Ser. No. US 2001-975883, filed on 12 Oct 2001, ABANDONED
Continuation of Ser. No. US 1999-445907, filed on 15 Dec 1999, ABANDONED
A 371 of International Ser. No. WO 1998-GB2109, filed on 16 Jul 1998, UNKNOWN
PRAI GB 1997-15306 19970718
DT Utility
FS APPLICATION
LREP GLAXOSMITHKLINE, Corporate Intellectual Property - UW2220, P.O. Box 1539, King of Prussia, PA, 19406-0939
CLMN Number of Claims: 21
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 483
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method for the treatment of **diabetes** mellitus and conditions associated with **diabetes** mellitus in a mammal, which method comprises administering an effective non-toxic and pharmaceutically acceptable amount of an insulin sensitiser and a sub-maximal amount of

an insulin secretagogue, to a mammal in need thereof; and a pharmaceutical composition for use in such method.

TI Treatment of **diabetes** with thiazolidinedione and sulphonylurea

AB A method for the treatment of **diabetes** mellitus and conditions associated with **diabetes** mellitus in a mammal, which method comprises administering an effective non-toxic and pharmaceutically acceptable amount of an insulin sensitiser and. . .

SUMM [0001] This invention relates to a method of treatment, in particular to a method for the treatment of **diabetes** mellitus, especially non-insulin dependent **diabetes** (NIDDM) (or Type 2 **diabetes**) and conditions associated with **diabetes** mellitus.

SUMM . . . known examples of insulin secretagogues. The sulphonylureas act as hvpoglycaemic agents and are used in the treatment of Type 2 **diabetes**. Examples of sulphonylureas include glibenclamide, glipizide, gliclazide, **glimepiride**, tolazamide and tolbutamide.

SUMM . . . relates to certain thiazolidinedione derivatives disclosed as having hypoglycaemic and hypolipidaemic activity. One particular thiazolidinedione disclosed in EP 0306228 is 5-[4-[2-(N-**methyl**-N-(2-**pyridyl**)amino)ethoxy]**benzyl**]**thiazolidine**-2,4-dione (hereinafter `Compound (I)`). WO94/05659 discloses certain salts of Compound (I) including the maleate salt.

SUMM . . . insulin secretagogue provides a particularly beneficial effect on glycaemic control, such combination is therefore particularly useful for the treatment of **diabetes** mellitus and conditions associated with **diabetes**. Lowering the dose of the insulin secretagogue in the presence of a full dose of insulin sensitising agent also has. . .

DETD [0010] Accordingly, the invention provides a method for the treatment of **diabetes** mellitus, especially Type 2 **Diabetes**, and conditions associated with **diabetes** in a mammal such as a human, which method comprises administering an effective non-toxic and pharmaceutically acceptable amount of an. . .

DETD . . . Compound (I), together with a sub-maximal amount of an insulin secretagogue for use in a method for the treatment of **diabetes** mellitus, especially Type 2 **diabetes** and conditions associated with **diabetes** mellitus.

DETD . . . Compound (I), and a sub-maximal amount of an insulin secretagogue in the manufacture of a composition for the treatment of **diabetes** mellitus, especially Type 2 **diabetes** and conditions associated with **diabetes** mellitus.

DETD . . . with an insulin secretagogue for use in reducing the likelihood, frequency and/or severity of hypoglycaemic episodes in the treatment of **diabetes** mellitus, especially Type 2 **diabetes** and conditions associated with **diabetes** mellitus, wherein the dose of the insulin secretagogue is a sub-maximal dose.

DETD . . . for the manufacture of a composition for reducing the likelihood, frequency and/or severity of hypoglycaemic episodes in the treatment of **diabetes** mellitus, especially Type 2 **diabetes** and conditions associated with **diabetes** mellitus, wherein the amount of the insulin secretagogue is sub-maximal.

DETD [0020] Other suitable thiazolidinedione insulin sensitisers include (+)-5-[[4-[(3,4-dihydro-6-hydroxy-2, 5, 7, 8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]**methyl**]-2,4-thiazolidinedione (or troglitazone), 5-[4-[(1-methylcyclohexyl)methoxy]**benzyl**]**thiazolidine**-2,4-dione (or ciglitazone), 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]**benzyl**]**thiazolidine**-2,4-dione (or pioglitazone) or 5-[(2-**benzyl**-2,3-dihydrobenzopyran)-5-ylmethyl)**thiazolidine**-2,4-dione (or englitazone)

DETD [0022] Suitable sulphonylureas include glibenclamide, glipizide,

gliclazide, **glimepiride** tolazamide and tolbutamide.

DETD [0025] In one particular aspect, the method comprises the administration of 2 to **12 mg** of Compound (I), especially when administered per day.

DETD [0026] Particularly, the method comprises the administration of 2 to 4, 4 to 8 or 8 to **12 mg** of Compound (I) per day.

DETD [0029] Particularly, the method comprises the administration of 8 to **12 mg** of Compound (I), especially when administered per day.

DETD [0041] When used herein the term `conditions associated with **diabetes**` includes those conditions associated with **diabetes** mellitus itself and complications associated with **diabetes** mellitus.

DETD [0042] `Conditions associated with **diabetes** mellitus itself` include hyperglycaemia, insulin resistance, including acquired insulin resistance. Further conditions associated with **diabetes** mellitus itself include hypertension and cardiovascular disease, especially atherosclerosis and conditions associated with insulin resistance. Conditions associated with insulin resistance include polycystic ovarian syndrome and steroid induced insulin resistance and gestational **diabetes**.

DETD [0043] `Complications associated with **diabetes** mellitus` includes renal disease, especially renal disease associated with Type 2 **diabetes**, neuropathy and retinopathy.

DETD [0044] Renal diseases associated with Type 2 **diabetes** include nephropathy, glomerulonephritis, glomerular sclerosis, hypertensive nephrosclerosis and end stage renal disease. Additional renal diseases associated with Type 2 **diabetes** include nephrotic syndrome.

DETD [0047] **Diabetes** mellitus is preferably Type 2 **diabetes**

.

DETD . . . insulin sensitiser is administered at its normal, appropriate dose, for example Compound (I) is administered at a dose selected from 2-**12 mg** per day, for example 1, 2, 4 or 8 mg per day.

DETD . . . the present invention also provides a pharmaceutical composition comprising an insulin sensitiser, such as Compound (I) and especially 2 to **12 mg** thereof, a sub-maximal amount of an insulin secretagogue and a pharmaceutically acceptable carrier therefor.

DETD [0053] Such compositions may be prepared by admixing an insulin sensitiser, such as Compound (I) and especially 2 to **12 mg** thereof, a sub-maximal amount of an insulin secretagogue and a pharmaceutically acceptable carrier therefor.

DETD . . . dosages, including unit dosages, of Compound (I) comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or **12 mg** of Compound (I).

DETD . . . other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, **methyl** cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats: emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous. . . almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example **methyl** or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

DETD . . . The present invention also provides a pharmaceutical composition comprising an insulin sensitiser, such as Compound (I) and especially 2 to **12 mg** thereof, a sub-maximal amount of an insulin secretagogue and a pharmaceutically acceptable carrier therefor, for use as an active therapeutic. . .

DETD [0070] The invention also provides the use of an insulin sensitiser,

such as Compound (I) and especially 2 to **12 mg** thereof, a sub-maximal amount of an insulin secretagogue for the manufacture of a medicament for the treatment of **diabetes** mellitus and conditions associated with **diabetes**.

DETD . . . particular, the present invention provides a pharmaceutical composition comprising an insulin sensitiser, such as Compound (I) and especially 2 to **12 mg** thereof, a sub-maximal amount of an insulin secretagogue and a pharmaceutically acceptable carrier therefor, for use in the treatment of **diabetes** and conditions associated with **diabetes**.

DETD [0074] A range of 8 to **12 mg** includes a range of 8.1 to 12, 8.2 to 12, 8.3 to 12, 8.4 to 12, 8.5 to 12, 8.6. . . to 12, 8.7 to 12, 8.8 to 12, 8.9 to 12, 9 to 12, 10 to 12 or 11 to **12 mg**.

CLM What is claimed is:

1. A method for the treatment of **diabetes** mellitus and conditions associated with **diabetes** mellitus in a mammal, which method comprises administering an effective non-toxic and pharmaceutically acceptable amount of an insulin sensitiser and. . .

3. A method according to claim 1, wherein the insulin secretagogue is glibenclamide, glipizide, gliclazide, **glimepiride**, tolazamide, tolbutamide, acetohexamide, carbutamide, chlorpropamide, glibornuride, gliquidone, glisentide, glisolamide, glisoxepide, glyclopyamide and glycylamide or repaglinide.

4. A method according to any one of claims 1 to 3, wherein the insulin sensitiser is 5-[4-[2-(N-**methyl**-N-(2-**pyridyl**)amino)ethoxy]**benzyl**]**thiazolidine**-2,4-dione (Compound I) or a tautomeric form thereof and/or a pharmaceutically acceptable derivative thereof.

5. A method according to any one of claims 1 to 4, which comprises the administration of 2 to **12 mg** of Compound (I).

. . . one of claims 1 to 5, which comprises the administration of 2 to 4, 4 to 8 or 8 to **12 mg** of Compound (I).

9. A method according to any one of claims 1 to 6, which comprises the administration of 8 to **12 mg** of Compound (I).

13. A method according to claim 1, wherein the insulin sensitiser is (+)-5-[[4-[(3,4-dihydro-6-hydroxy-2, 5, 7, 8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]**methyl**]-2,4-thiazolidinedione (or troglitazone), 5-[4-[(1-methylcyclohexyl)methoxy]**benzyl**]**thiazolidine**-2.4-dione (or ciglitazone), 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]**benzyl**]**thiazolidine**-2,4-dione (or pioglitazone) or 5-[(2-**benzyl**-2,3-dihydrobenzopyran)-5-ylmethyl)**thiazolidine**-2,4-dione (or englitazone); or a tautomeric form thereof and/or a pharmaceutically acceptable derivative thereof.

16. A composition according to claim 14 or claim 15, wherein the insulin secretagogue is glibenclamide, glipizide, gliclazide, **glimepiride**, tolazamide or tolbutamide, acetohexamide, carbutamide, chlorpropamide, glibornuride, gliquidone, glisentide, glisolamide, glisoxepide, glyclopyamide and glycylamide or repaglinide.

18. A composition according to any one of claims 14 to 17, which comprises 2 to **12 mg** of Compound (I).

. . . sensitiser, a sub-maximal amount of an insulin secretagogue and a pharmaceutically acceptable carrier therefor, for use in the treatment of **diabetes** mellitus and conditions associated with

diabetes mellitus.

. . . A composition according to any one of claims 14, 19 or 20, wherein the insulin sensitiser is (+)-5-[[4-[(3,4-dihydro-6-hydroxy-2, 5, 7, 8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]**methyl**]-2,4-thiazolidinedione (or troglitazone), 5-[4-[(1-methylcyclohexyl)methoxy]**benzyl**]**thiazolidine**-2,4-dione (or ciglitazone), 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]**benzyl**]**thiazolidine**-2,4-dione (or pioglitazone) or 5-[(2-**benzyl**-2,3-dihydrobenzopyran)-5-ylmethyl)**thiazolidine**-2,4-dione (or englitazone); or a tautomeric form thereof and/or a pharmaceutically acceptable derivative thereof.

L3 ANSWER 4 OF 15 USPATFULL on STN
AN 2003:134661 USPATFULL
TI Treatment of **diabetes** with thiazolidinedione, insulin secretagogue and alpha glucocidase inhibitor
IN Buckingham, Robin Edwin, Welwyn Garden City, UNITED KINGDOM
Smith, Stephen Alistair, Bramfield, UNITED KINGDOM
PA SmithKline Beecham p.l.c. (non-U.S. corporation)
PI US 2003092750 A1 20030515
AI US 2002-322982 A1 20021218 (10)
RLI Continuation of Ser. No. US 2001-989572, filed on 20 Nov 2001, ABANDONED Continuation of Ser. No. US 1999-445908, filed on 15 Dec 1999, ABANDONED A 371 of International Ser. No. WO 1998-GB2112, filed on 16 Jul 1998, UNKNOWN
PRAI GB 1997-15298 19970718
DT Utility
FS APPLICATION
LREP GLAXOSMITHKLINE, Corporate Intellectual Property - UW2220, P.O. Box 1539, King of Prussia, PA, 19406-0939
CLMN Number of Claims: 22
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 493
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method for the treatment of **diabetes** mellitus and conditions associated with **diabetes** mellitus in a mammal, which method comprises administering an effective non-toxic and pharmaceutically acceptable amount of an insulin sensitiser, an insulin secretagogueand an alpha glucosidase inhibitor antihyperglycaemic agent, to a mammal in need thereof; and composition for use in such method.
TI Treatment of **diabetes** with thiazolidinedione, insulin secretagogue and alpha glucocidase inhibitor
AB A method for the treatment of **diabetes** mellitus and conditions associated with **diabetes** mellitus in a mammal, which method comprises administering an effective non-toxic and pharmaceutically acceptable amount of an insulin sensitiser, an. . . .
SUMM [0001] This invention relates to a method of treatment, in particular to a method for the treatment of **diabetes** mellitus, especially non-insulin dependent **diabetes** (NIDDM) or Type 2 **diabetes** and conditions associated with **diabetes** mellitus.
SUMM . . . known examples of insulin secretagogues. The sulphonylureas act as antihyperglycaemic agents and are used in the treatment of Type 2 **diabetes**. Examples of sulphonylureas include glibenclamide, glipizide, gliclazide, **glimepiride**, tolazamide and tolbutamide.
SUMM . . . Alpha glucosidase inhibitor antihyperglycaemic agents, such as acarbose, emiglitate and miglitol, are commonly used in the treatment of Type 2 **diabetes**.
SUMM . . . relates to certain thiazolidinedione derivatives disclosed as

having antihyperglycaemic and antihyperlipidaemic activity. One particular thiazolidinedione disclosed in EP 0306228 is 5-[4-[2-(N-**methyl**-N-(2-**pyridyl**)amino)ethoxy]**benzyl**] **thiazolidine**-2,4-dione (hereinafter `Compound (I)`). WO94/05659 discloses certain salts of Compound (I) including the maleate salt.

DETD . . . by reference provides a particularly beneficial effect on glycaemic control, such combination is therefore particularly useful for the treatment of **diabetes** mellitus, especially Type 2 **diabetes**, and conditions associated with **diabetes** mellitus. The treatment is also indicated to proceed with minimum side effects.

DETD [0011] Accordingly, the invention provides a method for the treatment of **diabetes** mellitus, especially Type 2 **diabetes**, and conditions associated with **diabetes** mellitus, in a mammal such as a human, which method comprises administering an effective non-toxic and pharmaceutically acceptable amount of. . .

DETD . . . an insulin secretagogue and an alpha glucosidase inhibitor antihyperglycaemic agent, in the manufacture of a composition for the treatment of **diabetes** mellitus, especially Type 2 **diabetes** and conditions associated with **diabetes** mellitus.

DETD [0017] Other suitable thiazolidinedione insulin sensitisers include (+) -5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]**methyl**]-2,4-thiazolidinedione (or troglitazone), 5-[4-[(1-methylcyclohexyl)methoxy]**benzyl**] **thiazolidine**-2,4-dione (or ciglitazone), 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]**benzyl**]**thiazolidine**-2,4-dione (or pioglitazone) or 5-[(2-**benzyl**-2,3-dihydrobenzopyranyl)-5-ylmethyl)**thiazolidine**-2,4-dione (or englitazone)

DETD [0019] Suitable sulphonylureas include glibenclamide, glipizide, gliclazide, **glimepiride**, tolazamide and tolbutamide.

DETD [0024] In one particular aspect, the method comprises the administration of 2 to **12 mg** of Compound (I), especially when administered per day.

DETD [0025] Particularly, the method comprises the administration of 2 to 4, 4 to 8 or 8 to **12 mg** of Compound (I) per day.

DETD [0028] Particularly, the method comprises the administration of 8 to **12 mg** of Compound (I), especially when administered per day.

DETD [0039] When used herein the term `conditions associated with **diabetes**` includes conditions associated with **diabetes** mellitus itself and complications associated with **diabetes** mellitus. Also included in `conditions associated with **diabetes** ` are those conditions associated with the pre-diabetic state.

DETD [0041] `Conditions associated with **diabetes** mellitus itself` include hyperglycaemic, insulin resistance, including acquired insulin resistance. Further conditions associated with **diabetes** mellitus itself include hypertension and cardiovascular disease, especially atherosclerosis and conditions associated with,insulin resistance. Conditions associated with insulin resistance include polycystic ovarian syndrome and steroid induced insulin resistance and gestational **diabetes**.

DETD [0042] `Complications associated with **diabetes** mellitus` includes renal disease, especially renal disease associated with Type 2 **diabetes**, neuropathy and retinopathy.

DETD [0043] Renal diseases associated with Type 2 **diabetes** include nephropathy, glomerulonephritis, glomerular sclerosis, hypertensive nephrosclerosis and end stage renal disease. Additional renal diseases associated with Type 2 **diabetes** include nephrotic syndrome.

DETD [0045] **Diabetes** mellitus is preferably Type 2 **diabetes**

.

DETD . . . the present invention also provides a pharmaceutical

composition comprising an insulin sensitiser, such as Compound (I) and especially 2 to **12 mg** thereof, an insulin secretagogue and an alpha glucosidase inhibitor antihyperglycaemic agent and a pharmaceutically acceptable carrier therefor.

DETD [0056] Such compositions may be prepared by admixing an insulin sensitiser, such as Compound (I) and especially 2 to **12 mg** thereof, an insulin secretagogue and an alpha glucosidase inhibitor antihyperglycaemic agent and a pharmaceutically acceptable carrier therefor.

DETD . . . dosages, including unit dosages, of Compound (I) comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or **12 mg** of Compound (I).

DETD . . . other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, **methyl** cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminum stearate gel, hydrogenated edible fats: emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous. . . almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example **methyl** or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

DETD . . . The present invention also provides a pharmaceutical composition comprising an insulin sensitiser, such as Compound (I) and especially 2 to **12 mg** thereof, an insulin secretagogue and an alpha glucosidase inhibitor antihyperglycaemic agent and a pharmaceutically acceptable carrier therefor, for use as. . .

DETD [0077] The invention also provides the use of an insulin sensitiser, such as Compound (I) and especially 2 to **12 mg** thereof, an insulin secretagogue and an alpha glucosidase inhibitor antihyperglycaemic agent for the manufacture of a medicament for the treatment of **diabetes** mellitus and conditions associated with **diabetes** mellitus.

DETD . . . particular, the present invention provides a pharmaceutical composition comprising an insulin sensitiser, such as Compound (I) and especially 2 to **12 mg** thereof, an insulin secretagogue and an alpha glucosidase inhibitor antihyperglycaemic agent and a pharmaceutically acceptable carrier therefor, for use in the treatment of **diabetes** mellitus and conditions associated with **diabetes** mellitus.

DETD [0081] A range of 8 to **12 mg** includes a range of 8.1 to 12, 8.2 to 12, 8.3 to 12, 8.4 to 12, 8.5 to 12, 8.6. . . to 12, 8.7 to 12, 8.8 to 12, 8.9 to 12, 9 to 12, 10 to 12 or 11 to **12 mg**.

CLM What is claimed is:

1. A method for the treatment of **diabetes** mellitus and conditions associated with **diabetes** mellitus in a mammal, which method comprises administering an effective non-toxic and pharmaceutically acceptable amount of an insulin sensitiser, an. . .

2. A method according to claim 1, wherein the insulin secretagogue is glibenclamide, glipizide, gliclazide, **glimepiride**, tolazamide, tolbutamide, acetohexamide, carbutamide, chlorpropamide, glibornuride, gliquidone, glisentide, glisolamide, glisoxepide, glyclopyamide, glycylamide or repaglinide.

4. A method according to any one of claims 1 to 3, wherein the insulin sensitiser is 5-[4-(2-(N-**methyl**-N-(2-**pyridyl**)amino)ethoxy]**benzyl**]**thiazolidine**-2,4-dione (Compound I).

5. A method according to any one of claims 1 to 4, which comprises the administration of 2 to **12 mg** of Compound (I).

. . . one of claims 1 to 5, which comprises the administration of 2 to 4, 4 to 8 or 8 to **12 mg** of Compound (I).

9. A method according to any one of claims 1 to 6, which comprises the administration of 8 to **12 mg** of Compound (I).

13. A method according to claim 1, wherein the insulin sensitiser is (+) -5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]**methyl**]-2,4-thiazolidinedione (or troglitazone), 5- [4-[(1-methylcyclohexyl)methoxy]**benzyl**] **thiazolidine**-2,4-dione (or ciglitazone), 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]**benzyl**]**thiazolidine**-2,4-dione (or pioglitazone) or 5-[(2-**benzyl**-2,3-dihydrobenzopyranyl)-5-ylmethyl)**thiazolidine**-2,4-dione (or englitazone); or a pharmaceutically acceptable form thereof.

16. A composition according to claim 14 or claim 15, wherein the insulin secretagogue is glibenclamide, glipizide, gliclazide, **glimepiride**, tolazamide or tolbutamide, acetohexamide, carbutamide, chlorpropamide, glibornuride, gliquidone, glisentide, glisolamide, glisoxepide, glyclopyamide, glycylamide or repaglinide.

19. A composition according to any one of claims 14 to 17, which comprises 2 to **12 mg** of Compound (I).

. . . insulin secretagogue, an alpha glucosidase inhibitor antihyperglycaemic agent and a pharmaceutically acceptable carrier therefor, for use in the treatment of **diabetes** mellitus and conditions associated with **diabetes** mellitus.

. . . composition according to any one of claims 14, 20 or 21, wherein the insulin sensitiser is (+) -5-[[4-[(3,4-dihydro-6-hydroxy-2, 5, 7, 8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]**methyl**]-2,4-thiazolidinedione (or troglitazone), 5-[4-[(1-methylcyclohexyl)methoxy]**benzyl**]**thiazolidine** -2,4-dione (or ciglitazone), 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy] **benzyl**]**thiazolidine**-2,4-dione (or pioglitazone) or 5-[(2-**benzyl**-2,3-dihydrobenzopyranyl)-5-ylmethyl) **thiazolidine**-2,4-dione (or englitazone); or a pharmaceutically acceptable form thereof.

L3 ANSWER 5 OF 15 USPATFULL on STN
AN 2003:123367 USPATFULL
TI Method of treating metabolic disorders especially **diabetes**, or a disease or condition associated with **diabetes**
IN Gatlin, Marjorie Regan, Hoboken, NJ, United States
Ball, Michele Ann, Morris Plains, NJ, United States
Mannion, Richard Owen, Mount Arlington, NJ, United States
Karnachi, Anees Abdulquadar, Hillsborough, NJ, United States
Guitard, Christiane, Hegenheim, FRANCE
Allison, Malcolm, Basel, SWITZERLAND
PA Novartis AG, Basel, SWITZERLAND (non-U.S. corporation)
PI US 6559188 B1 20030506
AI US 2000-663264 20000915 (9)
PRAI US 2000-304196P 20000407 (60)
US 2000-240918P 20000309 (60)
US 1999-242911P 19990917 (60)
DT Utility
FS GRANTED
EXNAM Primary Examiner: Weddington, Kevin E.

LREP Thallemer, John D.
CLMN Number of Claims: 11
ECL Exemplary Claim: 1
DRWN 0 Drawing Figure(s); 0 Drawing Page(s)
LN.CNT 2176
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to a combination, such as a combined preparation or pharmaceutical composition, respectively, which comprises nateglinide (I) ##STR1##

or repaglinide and at least one other antidiabetic compound selected from the group consisting of thiazolidinedione derivatives (glitazones), sulfonyl urea derivatives and metformin for simultaneous, separate or sequential use in the prevention, delay of progression or treatment of diseases, especially metabolic disorders and in particular type 2 **diabetes** and diseases and conditions associated with **diabetes**; to a composition, respectively, which comprises nateglinide and a pharmaceutically acceptable carrier and to a process of making such composition; the use of such combination or composition for the preparation of a medicament for the prevention, delay of progression or treatment of metabolic disorders; a method of prevention, delay of progression or treatment of diseases in warm-blooded animals; the use of such combination or composition for the cosmetic treatment of a mammal in order to effect a cosmetically beneficial loss of body weight; and to a method of improving the bodily appearance of a warm-blooded animal.

TI Method of treating metabolic disorders especially **diabetes**, or a disease or condition associated with **diabetes**

AB . . . sequential use in the prevention, delay of progression or treatment of diseases, especially metabolic disorders and in particular type 2 **diabetes** and diseases and conditions associated with **diabetes**; to a composition, respectively, which comprises nateglinide and a pharmaceutically acceptable carrier and to a process of making such composition;. . .

SUMM . . . sequential use in the prevention, delay of progression or treatment of diseases, especially metabolic disorders and in particular type 2 **diabetes** and diseases and conditions associated with **diabetes**; the use of such combination for the preparation of a medicament for the prevention, delay of progression or treatment of. . .

SUMM The generally accepted aims in the treatment of **diabetes** are to provide relief from symptoms, improvement of the quality of life and prevention of both acute (hyperosmolar coma and ketoacidosis) and chronic complications (e.g. diabetic neuropathy, diabetic nephropathy and premature atherosclerosis). Type 2 **diabetes** is characterized by both increased peripheral insulin resistance and abnormal insulin secretion. At least two abnormalities of insulin secretion are. . . lost. Several metabolic, hormonal, and pharmacological entities are known to stimulate insulin secretion including glucose, amino-acids and gastrointestinal peptides. The **Diabetes** Control and Complications Trial (DCCT) performed in Type I IDDM subjects has established that lowering of blood glucose is associated with decreases in the onset and progression of diabetic microvascular complications (**Diabetes** Control and Complications Trial Research Group; N. Engl. J. Med. 1993, 329, 977-986). Therefore, one therapeutic focus is on optimizing and potentially normalizing glycemic control in subjects with type 2 **diabetes**. Presently available oral agents fail to meet this therapeutic challenge in some patient subgroups, result sometimes in side-effects or are. . .

SUMM . . . use, particularly in the prevention, delay of progression or treatment of diseases, especially metabolic disorders and in particular

type 2 **diabetes** mellitus and diseases and conditions associated with **diabetes** mellitus. Such a combination is preferably a combined preparation or a pharmaceutical composition.

SUMM In particular, the present invention relates to a method of treating metabolic disorders, more especially **diabetes** and in particular type 2 **diabetes** mellitus, or a disease or condition associated with **diabetes** comprising administering to a warm-blooded animal in need thereof a jointly therapeutically effective amount of a combined preparation comprising nateglinide. . .

SUMM "Diseases and conditions associated with **diabetes** mellitus" as defined in this application comprise, but are not restricted to hyperglycemia, hyperinsulinaemia, hyperlipidaemia, insulin resistance, impaired glucose metabolism,. . . diabetic nephropathy, glomerulosclerosis, diabetic neuropathy, erectile dysfunction, premenstrual syndrome, vascular restenosis and ulcerative colitis. Furthermore, "diseases and conditions associated with **diabetes** mellitus" comprise, but are not restricted to: coronary heart disease, hypertension, angina pectoris, myocardial infarction, stroke, skin and connective tissue. . .

SUMM . . . Moreover, the term "prevention" means prophylactic administration of such combination to patients being in a pre-stage of the disease, especially **diabetes**, to be treated. The term "delay of progression" used herein means administration of the combination, such as a combined preparation or pharmaceutical composition, to patients being in a pre-stage of the disease, especially **diabetes**, to be treated in which patients a pre-form of the corresponding disease is diagnosed. The term "method of treating" used. . .

SUMM . . . derivative is, for example, glisoxepid, glyburide, acetohexamide, chloropropamide, glibornuride, tolbutamide, tolazamide, glipizide, carbutamide, gliquidone, glyhexamide, phenbutamide or tolcyclamide; and preferably **glimepiride** or gliclazide.

SUMM Lower alkyl is, if not stated otherwise, preferably ethyl or, most preferably, **methyl**.

SUMM Nateglinide (EP 196222, EP 526171, U.S. Pat. Nos. 5,463,116 and 5,488,150), 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-**methyl**-1-butyl}-aminocarbonylmethyl]benzoic acid (repaglinide, U.S. Pat. No. 5,216,167--also known as (S)-2-ethoxy-4-{2-[[3-**methyl**-1-[2-(1-piperidinyl)phenyl]butyl]-amino]-2-oxoethyl}benzoic acid); 5-{[4-(2-(5-ethyl-2-**pyridyl**)ethoxy)phenyl]-**methyl**}-**thiazolidine**-2,4-dione (pioglitazone, EP 0 193 256 A1), 5-{[4-(2-(**methyl**-2-pyridinyl-amino)-ethoxy)phenyl]**methyl**}-**thiazolidine**-2,4-dione (rosiglitazone, EP 0 306 228 A1), 5{-[4-((3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy)-phenyl]-**methyl**}-**thiazolidine**-2,4-dione (troglitazone, EP 0 139 421), (S)-((3,4-dihydro-2-(phenyl-**methyl**)-2H-1-benzopyran-6-yl)**methyl**-**thiazolidine**-2,4-dione (englitazone, EP 0 207 605 B1), 5-(2,4-dioxothiazolidin-5-ylmethyl)-2-methoxy-N-(4-trifluoromethylbenzyl)benzamide (KRP297, JP 10087641-A), 5-[6-(2-fluoro-benzyloxy)naphthalen-2-ylmethyl]**thiazolidine**-2,4-dione (MCC555, EP 0 604 983 B1), 5-{[4-(3-(5-**methyl**-2-phenyl-4-oxazolyl)-1-oxopropyl)-phenyl]-**methyl**}-**thiazolidine**-2,4-dione (darglitazone, EP 0 332 332), 5-(2-naphthylsulfonyl)-**thiazolidine**-2,4-dione (AY-31637, U.S. Pat. No. 4,997,948) and 5-{[4-(1-**methyl**-cyclohexyl)methoxy)-phenyl]**methyl**}-**thiazolidine**-2,4-dione (ciglitazone, U.S. Pat. No. 4,287,200) are generically and specifically disclosed in the documents cited in brackets beyond each substance, in. . .

SUMM . . . 6, or analogous to Examples 27 or 28 on page 24 of EP 0 207 605 B1; and darglitazone and 5-{4-[2-(5-**methyl**-2-phenyl4-oxazolyl)-ethoxy)]**benzyl**}-**thiazolidine**-2,4-dione (BM-13.1246)

can be formulated as disclosed on page 8, line 42 to line 54 of EP 0 332 332 B1.. . .

SUMM . . . the trademark AZUGLUCON.TM. or EUGLUCON.TM.. Tolbutamide can be administered in the form as it is launched under the trademark ORABET, **glimepiride** as launched under the trademark AMARYL.TM., gliclazide as launched under the trademark DIAMICRON.TM., glibornuride as launched under the trademark GLUBORID.TM.. . .

SUMM . . . either as a single dose or in divided doses twice daily. The best responses with rosiglitazone in the treatment of **diabetes** are observed with 4 mg twice daily. The recommended dose for pioglitazone taken as a single drug is 15 mg,. . .

SUMM The nature of **diabetes** and related diseases or conditions is multifactorial. Under certain circumstances, drugs with different mechanisms of action may be combined. However,. . .

SUMM . . . surprising prolongation of efficacy, a broader variety of therapeutic treatment and surprising beneficial effects on diseases and conditions associated with **diabetes**, e.g. less gain of weight.

SUMM . . . thereof, results in a more effective prevention or preferably treatment of diseases, especially metabolic disorders, and in particular type 2 **diabetes** mellitus and diseases and conditions associated with **diabetes** mellitus. In particular, it can be shown by established test models and especially those test models described herein that the. . . pharmaceutically acceptable salt thereof, results in a more effective prevention or preferably treatment of diseases, especially metabolic disorders, more especially **diabetes** and in particular type 2 **diabetes** mellitus, and diseases and conditions associated with **diabetes**.

SUMM . . . broader variety of therapeutic treatment and surprising beneficial effects, e.g. less increase of weight, on diseases and conditions associated with **diabetes** mellitus, for a number of combinations as described herein. Moreover, for a human patient, especially for elderly people, it is. . .

SUMM Clinical Double-blind, Randomized, Parallel-group Studies in Subjects with Type 2 **Diabetes** Inadequately Controlled on Diet or Monotherapy and Diet Alone

SUMM . . . claimed combinations, such as the combined preparations or pharmaceutical compositions, respectively. The beneficial effects on diseases and conditions associated with **diabetes** mellitus as defined in this application can be determined directly through the results of these studies or by changes in. . .

SUMM . . . combination of nateglinide and metformin or the corresponding hydrochloride salt on glycemic control. Subjects with a diagnosis of type 2 **diabetes** who have not achieved near normoglycemia (HbA.sub.1c<6.8%) on diet only are chosen for this trial. The effects on glycemic control. . . same diet as in the period before treatment. Measures of glycemic control are validated surrogate endpoints for the treatment of **diabetes**. HbA.sub.1c is the single most reliable measurement for assessing glycemic control (D. Goldstein et al, Tests of Glycemia in **Diabetes**; **Diabetes** Care 1995, 18(6), 896-909) and is the primary response variable in these studies. Since glycosylation of hemoglobin is determined by. . .

SUMM . . . invention can be used for the prevention, delay of progression and preferably the treatment of metabolic disorders and in particular **diabetes**, especially type 2 **diabetes** mellitus and diseases and conditions associated with **diabetes**. The combinations of the present invention can also be used for the prevention and preferably the treatment of other diseases.

SUMM . . . of glitazones, sulfonyl urea derivatives and metformin results in a beneficial, especially a synergistic, therapeutic effect, especially on type 2 **diabetes**, and also in additional benefits such as a decrease of **diabetes**-related mortality, a surprising prolongation of efficacy of the drug (such delaying the eventual need

for insulin), a broader variety of therapeutic treatment, maintaining the target blood glucose level in type 2 **diabetes** patients, providing a good initial blood glucose control in type 2 **diabetes** patients, only modest changes in fasting plasma glucose level, and further surprising beneficial effects, comprising e.g. less or no gain. . . particular, the further surprising beneficial effects can also be observed during the treatment of metabolic disorders other than type 2 **diabetes** and during the treatment of diseases and conditions associated with type 2 **diabetes**. Further benefits are that lower doses of the individual drugs to be combined according to the present invention can be. . .

SUMM . . . also the surprising beneficial effects are observed especially in human subjects suffering from a more severe form of type 2 **diabetes**, i.e. human subjects having an elevated HbA.sub.1c (glycosylated haemoglobin) value at baseline of greater 8% and more particular in human. . .

SUMM . . . combined preparation for simultaneous, separate or sequential use in the prevention or treatment of diseases, especially metabolic disorders, more especially **diabetes** and in particular type 2 **diabetes** mellitus, and diseases and conditions associated with **diabetes**.

SUMM b) **pyridyl**, lower alkyl-**pyridyl**, N-lower alkyl-N-pyridylamino or halogenphenyl,

SUMM . . . in 6-position of the naphthyl radical and is --XR.sub.4, in which X is oxygen; R.sub.4 is lower alkyl, most preferably **methyl**, which is substituted by halogenphenyl, most preferably 2-fluorophenyl. R.sub.2 and R.sub.3 are both hydrogen.

SUMM . . . R.sub.3 is arylsulfonyl, wherein preferably aryl is phenyl which is unsubstituted or substituted by halogen, preferably fluorine, lower alkyl, preferably **methyl**, or lower alkoxy, preferably methoxy; or naphthyl. Most preferably R.sub.3 is phenyl-sulfonyl which is unsubstituted.

SUMM . . . is hydroxy lower alkyl, preferably 2-hydroxyethyl, substituted by oxazolyl, preferably 4-oxazolyl, which is substituted by phenyl and lower alkyl, preferably **methyl**. R.sub.2 and R.sub.3 are both hydrogen.

SUMM . . . glitazone is represented by formula (IIa), in which R.sub.1 is XR.sub.4, X is oxygen and R.sub.4 is lower alkyl, preferably **methyl** or ethyl and most preferably **methyl**; R.sub.2 is trifluoromethylphenyl-lower alkyl carbamoyl, preferably trifluoromethylbenzylcarbamoyl; and R.sub.3 is hydrogen.

SUMM . . . glitazone is represented by formula (IIa), in which R.sub.1 is XR.sub.4, X is oxygen and R.sub.4 is lower alkyl, preferably **methyl** or ethyl and most preferably **methyl**, substituted by **pyridyl** or lower alkyl-**pyridyl**. More preferably lower alkyl is substituted by lower alkyl-2-**pyridyl** and most preferably by ethyl-2-**pyridyl**. R.sub.2 and R.sub.3 are hydrogen.

SUMM . . . glitazone is represented by formula (IIa), in which R.sub.1 is XR.sub.4, X is oxygen and R.sub.4 is lower alkyl, preferably **methyl**, which is substituted by dihydrobenzopyranyl, preferably 3,4-dihydro-2H-1-benzopyran-2-yl, which is unsubstituted or, preferably, substituted by lower alkyl, preferably **methyl** or ethyl, and hydroxy. Most preferably X is oxygen, R.sub.4 is **methyl**, which is substituted by 3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl. R.sub.2 and R.sub.3 are hydrogen.

SUMM . . . alkyl substituted by cycloalkyl, preferably C.sub.5-C.sub.7cycloalkyl, more preferably cyclohexyl, which is unsubstituted or substituted by lower alkyl, preferably ethyl or **methyl** and more preferably **methyl**. R.sub.2 and R.sub.3 are hydrogen.

SUMM . . . R.sub.1 is XR.sub.4, X is oxygen and R.sub.4 is lower alkyl,

preferably ethyl, which is substituted by N-lower alkyl-N-pyridylamino, preferably N-**methyl**-N-pyridylamino and most preferably N-**methyl**-N-2-pyridylamino. R.sub.2 and R.sub.3 are hydrogen.

SUMM . . . oxygen or carbonyl and R.sub.4 is lower alkyl, preferably ethyl, which is substituted by oxazolyl substituted by lower alkyl, preferably **methyl**, and unsubstituted phenyl. R.sub.2 and R.sub.3 are hydrogen.

SUMM In a further preferred embodiment of the invention the glitazone is 5-(2-naphthylsulfonyl)-**thiazolidine**-2,4-dione.

SUMM . . . glitazone according to all aspects of the present invention is selected from the group consisting of englitazone, darglitazone, ciglitazone, AY-31637, 5-{[4-(2-(1-indolyl)ethoxy)phenyl]**methyl**}-**thiazolidine**-2,4-dione (DRF2189), 5-{[4-(2-(2,3-dihydroindol-1-yl)ethoxy)phenyl]**methyl**}-**thiazolidine**-2,4-dione, BM-13.1246, bis{4-[(2,4-dioxo-5thiazolidinyl)**methyl**]phenyl}methane (YM268), 5-{4-[2-(5-**methyl**-2-phenyl-4-oxazolyl)-2-hydroxyethoxy]**benzyl**}-**thiazolidine**-2,4-dione (AD-5075), 5-[3-(4-chlorophenyl])-2-propynyl]-5-phenylsulfonyl)**thiazolidine**-2,4-dione, 5-[3-(4-chlorophenyl])-2-propynyl]-5-(4-fluorophenylsulfonyl)**thiazolidine**-2,4-dione, 5-[4-(1-phenyl-1-cyclopropanecarbonylamino)**benzyl**]-**thiazolidine**-2,4-dione (DN-108) and their pharmaceutically acceptable salts.

SUMM . . . to provide a pharmaceutical composition comprising an amount, which is jointly therapeutically effective against metabolic disorders, in particular type 2 **diabetes** mellitus or a disease or condition associated with **diabetes** mellitus, of (i) nateglinide or repaglinide or in each case a pharmaceutically acceptable salt thereof and (ii) and at least. . .

SUMM . . . preparation of a medicament for the prevention, delay of progression or treatment of metabolic disorders, in particular of type 2 **diabetes** mellitus or a disease or condition associated with **diabetes** mellitus. In particular, this further aspect of the present invention relates to the use of a pharmaceutical composition comprising nateglinde. . . thereof for the preparation of a pharmaceutical preparation for the prevention or treatment of diseases, especially metabolic disorders, more especially **diabetes** and in particular type 2 **diabetes** mellitus, and diseases and conditions associated with **diabetes**.

SUMM . . . tissue disorders, foot ulcerations, metabolic acidosis, arthritis, osteoporosis and in particular conditions of impaired glucose tolerance and especially type 2 **diabetes**.

SUMM . . . pharmaceutical formulations (compositions) for administration to mammals suffering from or at risk for diseases having the characteristics of type 2 **diabetes**. It will be understood that any statistically significant attenuation in the disease symptoms of type 2diabetes pursuant to the treatment. . .

SUMM . . . therapies of the present invention can also be administered to mammals suffering from diseases having the characteristics of type 2 **diabetes** in aerosol form. It is expected that lower amounts of antidiabetic drugs, or disease suppressive fragments or analogs thereof will be required using aerosol administration for treating or preventing type 2 **diabetes** as has been found in the treatment of other allergic disease states. The amounts of anti-diabetic drugs or analogs thereof. . .

SUMM The combination of compounds of the present invention is useful in the treatment of **diabetes**. For these purposes, the combinations of the present invention may be administered orally, parenterally (including subcutaneous injections, intravenous, intramuscular, intrasternal. . .

SUMM . . . of the present invention there is further provided a method of treating and a pharmaceutical composition for treating obesity and

diabetes. The treatment involves administering to a patient in need of such treatment a pharmaceutical composition comprising a pharmaceutical carrier and. . .

SUMM . . . prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing **benzyl** alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the. . .

SUMM . . . sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, **methyl** and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

SUMM . . . present invention is a method of treating a warm-blooded animal, especially a human, having metabolic disorders, in particular type 2 **diabetes** mellitus or a disease or condition associated with **diabetes** mellitus, comprising administering to the animal a combination of nateglinide or repaglinide and at least one other antidiabetic compound selected. . .

SUMM In particular, the present invention relates to a method of treating **diabetes** or a disease or condition associated with **diabetes** comprising administering to a warm-blooded animal in need thereof jointly therapeutically effective amounts of nateglinide in free or pharmaceutically acceptable. . . or substituted by 2,4-dioxo-5-thiazolidinyl; or lower alkyl or hydroxy lower alkyl, unsubstituted or substituted by a) indole or 2,3-dihydroindole, b) **pyridyl**, lower alkyl-**pyridyl**, N-lower alkyl-N-pyridylamino or halogenphenyl, c) dihydrobenzopyranyl, which is unsubstituted or substituted by hydroxy and lower alkyl, d) oxazolyl, which is. . . this method, the glitazone is selected from the group consisting of englitazone, darglitazone, ciglitazone, DRF2189, BM-13.1246, AY-31637, YM268, AD-5075, DN-108, 5-{[4-(2-(2,3-dihydroindol-1-yl)ethoxy)phenyl]**methyl**}-**thiazolidine**-2,4-dione, 5-[3-(4-chloro-phenyl])-2-propynyl]-5-phenylsulfonyl) **thiazolidine**-2,4-dione, and 5-[3-(4-chlorophenyl])-2-propynyl]-5-(4-fluorophenylsulfonyl)**thiazolidine**-2,4-dione or a pharmaceutically acceptable salt therof. In a second more preferred embodiment of this method, the glitazone is selected from. . .

SUMM Especially, the present invention relates to a method of treating **diabetes** or a disease or condition associated with **diabetes** comprising administering to a warm-blooded animal in need thereof jointly therapeutically effective amounts of nateglinide in free or pharmaceutically acceptable. . . a pharmaceutically acceptable salt thereof. This particular embodiment of the invention relates especially to a method of treating type 2 **diabetes** patients by using an effective amount of a combination of at least one short-acting hypoglycemic agent with at least one. . . acting hypoglycemic agent is metformin. In an alternate preferred embodiment, the long acting hypoglycemic agent is a glitazone, most preferably 5-(2-naphthylsulfonyl)-**thiazolidine**-2,4-dione; rosiglitazone, pioglitazone, troglitazone, MCC555; T-174; KRP297; englitazone, darglitazone, ciglitazone, AY-31637, 5-{[4-(2-(1-indolyl)ethoxy)phenyl] **methyl**}-**thiazolidine**-2,4-dione (DRF2189), 5-{[4-(2-(2,3-dihydroindol-1-yl)ethoxy)phenyl]**methyl**}-**thiazolidine**-2,4-dione, BM-13.1246, bis{4-[(2,4-dioxo-5-thiazolidinyl)**methyl**]phenyl}methane (YM268), 5-{4-[2-(5-**methyl**-2-phenyl-4-oxazolyl)-2-hydroxyethoxy]**benzyl**}-**thiazolidine**-2,4-dione (AD-5075), 5-[3-(4-chlorophenyl])-2-propynyl]-5-phenylsulfonyl)**thiazolidine**-2,4-dione, 5-[3-(4-chlorophenyl])-2-propynyl]-5-(4-fluorophenylsulfonyl) **thiazolidine**-2,4-dione; or 5-[4-(1-phenyl-1-cyclopropanecarbonylamino)-**benzyl**]-**thiazolidine** -2,4-dione (DN-108); or a pharmaceutically acceptable salt thereof. In

the present embodiment, the short acting hypoglycemic and the long acting hypoglycemic. . .

SUMM . . . preferably about 5 to 100, mg/kg body weight of the warm-blooded animal. If the antidiabetic thiazolidinedione is T-174, KRP297, AD-5075, 5-[3-(4-chlorophenyl])-2-propynyl]-5-phenylsulfonyl)-**thiazolidine**-2,4-dione or 5-[3-(4-chlorophenyl])-2-propynyl]-5-(4-fluoro-phenylsulfonyl)**thiazolidine**-2,4-dione, the dosage of said compound is preferably in the range of about 0.1 to 2500, more preferably about 0.5 to. . .

SUMM . . . to 3500, more preferably 250 to 3000, for example 500, 1000, 1500, 2000, 2500, mg/day. If the sulfonyl urea derivative **glimepiride** is chosen as active ingredient and the warm-blooded animal being is a human of about 70 kg body weight, the. . .

SUMM . . . first by Emil A. Werner and James Bell, J. Chem. Soc. 121, 1922, 1790-1794. The preparation of DRF2189 and of 5-{[4-(2-(2,3-dihydroindol-1-yl)-ethoxy)phenyl]**methyl**}-**thiazolidine**-2,4-dione is described in B. B. Lohray et al., J. Med. Chem. 1998, 41, 1619-1630; Examples 2d and 3g on pages 1627 and 1628. The preparation of 5-[3-(4-chlorophenyl])-2-propynyl]-5-phenylsulfonyl)-**thiazolidine**-2,4-dione and the other compounds in which A is phenylethynyl mentioned herein can be carried out according to the methods described. . .

SUMM . . . invention is to provide a pharmaceutical composition that is effective for the treatment or prevention of metabolic disorders, more especially **diabetes** and in particular type 2 **diabetes** mellitus, or a disease or condition associated with **diabetes**.

SUMM The present invention also relates to a method for the treatment or prophylaxis of **diabetes** or a disease or condition associated with **diabetes** by administering to a warm-blooded animal in need thereof a pharmaceutical composition that contains a therapeutically effective amount of nateglinide. . .

SUMM . . . salt results in a more effective prevention, delay of progression or preferably treatment of diseases, especially metabolic disorders, more especially **diabetes** and in particular type 2 **diabetes** mellitus, and diseases and conditions associated with **diabetes**.

SUMM . . . tissue disorders, foot ulcerations, metabolic acidosis, arthritis, osteoporosis and in particular conditions of impaired glucose tolerance and especially type 2 **diabetes**.

SUMM . . . improving the bodily appearance of a mammal, including man, especially man suffering from a metabolic disorder, in particular type 2 **diabetes**, which comprises orally administering to said mammal (i) a combination, e.g. as a combined preparation or as a composition, as. . . especially a human being. Overweight is one of the risk factors for developing a metabolic disorder, in particular type 2 **diabetes**, and at the same time often the result of such a metabolic disorder, especially type 2 **diabetes**. Furthermore, a number of antidiabetics are known to cause weight gain. Hence, humans suffering from metabolic disorders, especially type 2 **diabetes**, are often faced with overweight. Therefore, the cosmetically beneficial loss of body weight can be effected especially in humans suffering from a metabolic disorder, such as type 2 **diabetes**. The combinations, e.g. a combined preparation or a composition, and compositions described herein independently of each other can also be used to replace or complement an antidiabetic drug taken by a human suffering from type 2 **diabetes** in order to prevent, for cosmetic reasons, a further increase of the body weight.

DETD

nateglinide 60 mg
lactose monohydrate 141.5 mg
microcrystalline cellulose 71 mg

Povidone **12 mg**
croscarmellose sodium 18.4 mg
magnesium stearate 5.7 mg
colloidal silicon dioxide 6.4 mg
opadry pink 9 mg

CLM What is claimed is:

9. The composition according to claim 1 which is used to treat **diabetes**.

10. The composition according to claim 9 wherein the **diabetes** is type 2 **diabetes**.

L3 ANSWER 6 OF 15 USPATFULL on STN
AN 2003:106732 USPATFULL
TI Combinations comprising a beta-agonist and a further antidiabetic agent
IN Sanders Arch, Jonathan Robert, Welwyn Garden City, UNITED KINGDOM
PA SmithKline Beecham p.l.c. (non-U.S. corporation)
PI US 2003073644 A1 20030417
AI US 2002-243164 A1 20020913 (10)
RLI Continuation of Ser. No. US 2001-831651, filed on 11 Jul 2001, ABANDONED A 371 of International Ser. No. WO 1999-GB3755, filed on 11 Nov 1999, UNKNOWN
PRAI GB 1998-24789 19981111
GB 1998-24791 19981111
GB 1998-24790 19981111
DT Utility
FS APPLICATION
LREP GLAXOSMITHKLINE, Corporate Intellectual Property - UW 2220, P.O. Box 1539, King of Prussia, PA, 19406-0939
CLMN Number of Claims: 18
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 769
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method for the treatment of **diabetes** mellitus and conditions associated with **diabetes** mellitus in a mammal such as a human, which method comprises administering an effective, non-toxic and pharmaceutically acceptable amount of a beta agonist and another antidiabetic agent, to a mammal in need thereof.
AB A method for the treatment of **diabetes** mellitus and conditions associated with **diabetes** mellitus in a mammal such as a human, which method comprises administering an effective, non-toxic and pharmaceutically acceptable amount of. . .
SUMM [0001] This invention relates to a method of treatment, in particular to a method for the treatment of **diabetes** mellitus, especially non-insulin dependent **diabetes** (NIDDM) or Type 2 **diabetes** and conditions associated with **diabetes** mellitus and to compositions for use in such method.
SUMM . . . agents (or alpha glucosidase inhibitors) and biguanide antihyperglycaemic agents (or biguanides) are commonly used in the treatment of Type 2 **diabetes**. Acarbose, voglibose, emiglitate and miglitol are examples of alpha glucosidase inhibitors. 1,1-Dimethylbiguanidine (or metformin) is a particular example of a. . .
SUMM . . . known examples of insulin secretagogues. The sulphonylureas act as hypoglycaemic agents and are used in the treatment of Type 2 **diabetes**. Examples of sulphonylureas include glibenclamide (or glyburide), glipizide, gliclazide, **glimepiride**, tolazamide and tolbutamide.
SUMM . . . relates to certain thiazolidinedione derivatives disclosed as having antihyperglycaemic and hypolipidaemic activity. One particular

thiazolidinedione disclosed in EP 0306228 is 5-[4-[2-(N-**methyl**-N-(2-**pyridyl**)amino)ethoxy]**benzyl**]**thiazolidine**-2,4-dione (hereinafter `Compound (I)`). WO94/05659 discloses certain salts of Compound (1) including the maleate salt at example 1 thereof.

SUMM [0010] or a salt thereof, in which R represents hydrogen atom or **methyl**, R.sup.1 stands for hydrogen atom, halogen atom, hydroxy, benzyloxy, amino or hydroxymethyl, R.sup.2 stands for hydrogen atom, hydroxymethyl, NHR.sup.3, SO.sub.2NR.sup.4R.sup.4, or nitro, wherein R.sup.3 is hydrogen atom, **methyl**, SO.sub.2R.sup.5, formyl or CONHR.sup.6,, with R.sup.5 being a lower alkyl, **benzyl** or NR.sup.4R.sup.4, and R.sup.6, being hydrogen atom or lower alkyl, and R.sup.4 and R.sup.4, may be identical with or different from each other and stand each for hydrogen atom, lower alkyl or **benzyl**, R.sup.6 represents hydrogen atom or lower alkyl, X stands for a secondary nitrogen atom, oxygen atom, sulfur atom or methylene. . .

SUMM . . . stated to have beta 3 adrenoreceptor agonist activity and are disclosed as being useful for the treatment and prevention of **diabetes**, hyperlipidaemia and obesity.

SUMM . . . beneficial effect on glycaemic control and that such combination is therefore suggested to be particularly useful for the treatment of **diabetes** mellitus, especially Type 2 **diabetes** and conditions associated with **diabetes** mellitus. Such combinations will provide improved blood glucose regulation without introducing unacceptable side-effects. In particular, combination of the beta 3-adrenoceptor. . .

DETD [0014] Accordingly, the invention provides a method for the treatment of **diabetes** mellitus, especially Type 2 **diabetes** and conditions associated with **diabetes** mellitus in a mammal such as a human, which method comprises administering an effective, non-toxic and pharmaceutically acceptable amount of. . .

DETD . . . aspect the invention provides a beta agonist and another antidiabetic agent, for use in a method for the treatment of **diabetes** mellitus, especially Type 2 **diabetes** and conditions associated with **diabetes** mellitus.

DETD . . . a beta agonist and another antidiabetic agent for use in the manufacture of a composition for the treatment of obesity, **diabetes** mellitus, especially Type 2 **diabetes** and conditions associated with **diabetes** mellitus.

DETD [0025] Suitable sulphonylureas include glibenclamide, glipizide, gliclazide, **glimepiride**, tolazamide and tolbutamide. Further sulphonylureas include acetohexamide, carbutamide, chlorpropamide, glibomuride, gliquidone, glisentide, glisolamide, glisoxepide, glyclopyamide and glycylamide. Also included is. . .

DETD [0029] Other suitable thiazolidinedione insulin sensitisers include (+)-5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]**methyl**]-2,4-thiazolidinedione (or troglitazone), 5-[4-[(1-methylcyclohexyl)methoxy]**benzyl**]**thiazolidine**-2,4-dione (or ciglitazone), 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]**benzyl**]**thiazolidine**-2,4-dione (or pioglitazone) or 5-[(2-**benzyl**-2,3-dihydrobenzopyran)-5-ylmethyl)**thiazolidine**-2,4-dione (or englitazone).

DETD [0030] A particular thiazolidinedione insulin sensitiser is 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]**benzyl**]**thiazolidine**-2,4-dione (or pioglitazone).

DETD [0031] A particular thiazolidinedione insulin sensitiser is (+)-5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]**methyl**]-2,4-thiazolidinedione (or troglitazone).

DETD [0045] N-**methyl**-3-[2-[2-(9H-carbazol-2-yloxy)ethylamino]-1-hydroxyethyl]benzenesulfonamide,

DETD [0046] N-**methyl**-[5-[2-[2-(9H-carbazol-2-yloxy)ethylamino]-1-

hydroxyethyl]-2-hydroxy]benzenesulfonamide,

DETD [0090] (R)-N-**methyl**-[5-[2-[2-(9H-carbazol-2-yloxy)ethylamino]-1-hydroxyethyl]-2-hydroxy]benzenesulfonamide,

DETD [0106] N'-[5-[2-[2-(9H-carbazol-2-yloxy)ethylamino]-1-hydroxyethyl]-2-aminophenyl]-N-**benzyl**-N-methylsulfamide,

DETD [0110] N'-[5-[2-[2-(9H-carbazol-2-yloxy)ethylamino]-1-hydroxyethyl]-2-hydroxyphenyl]-N-**benzyl**-N-methylsulfamide,

DETD [0146] When used herein the term `conditions associated with **diabetes**` includes those conditions associated with the pre-diabetic state, conditions associated with **diabetes** mellitus itself and complications associated with **diabetes** mellitus.

DETD [0148] `Conditions associated with **diabetes** mellitus itself` include hyperglycaemia, insulin resistance, including acquired insulin resistance and obesity. Further conditions associated with **diabetes** mellitus itself include hypertension and cardiovascular disease, especially atherosclerosis and conditions associated with insulin resistance. Conditions associated with insulin resistance include polycystic ovarian syndrome and steroid induced insulin resistance and gestational **diabetes**.

DETD [0149] `Complications associated with **diabetes** mellitus` includes renal disease, especially renal disease associated with Type 2 **diabetes**, neuropathy and retinopathy.

DETD [0150] Renal diseases associated with Type 2 **diabetes** include nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal disease.

DETD [0152] **Diabetes** mellitus is preferably Type 2 **diabetes**

.

DETD . . . a suitable amount of gliquidone is in the range of from 15 to 180 mg. Also a suitable amount of **glimepiride** is 1 to 6mg and a suitable amount of glipentide is 2.5 to 20 mg.

DETD [0171] In one particular aspect, the composition comprises 2 to **12 mg** of Compound (1).

DETD [0172] Suitably the composition comprises 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or **12 mg** of Compound (I).

DETD [0173] Particularly, the composition comprises 2 to 4, 4 to 8 or 8 to **12 mg** of Compound (I).

DETD [0177] Particularly, the composition comprises 8 to **12 mg** of Compound (I).

DETD . . . composition comprising a beta agonist, another antidiabetic agent and a pharmaceutically acceptable carrier therefor, for use in the treatment of **diabetes** mellitus, especially Type 2 **diabetes** and conditions associated with **diabetes** mellitus.

DETD . . . other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, **methyl** cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous. . . almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example **methyl** or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

DETD . . . sodium, dextrates, dextrin, dextrose, ethylcellulose, gelatin, liquid glucose, guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium aluminium silicate, maltodextrin, **methyl** cellulose, polymethacrylates, polyvinylpyrrolidone, pregelatinised starch, sodium alginate, sorbitol, starch, syrup, tragacanth.

DETD . . . include alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium, colloidal silicon dioxide, croscarmellose

sodium, crospovidone, guar gum, magnesium aluminium silicate, microcrystalline cellulose, **methyl** cellulose, polyvinylpyrrolidone, polacrilin potassium, pregelatinised starch, sodium alginate, sodium lauryl sulphate, sodium starch glycollate.

CLM What is claimed is:
1. A method for the treatment of **diabetes** mellitus and conditions associated with **diabetes** mellitus in a mammal such as a human, which method comprises administering an effective, non-toxic and pharmaceutically acceptable amount of. . .
9. A method according to claim 7 or claim 8, wherein the sulphonylurea is selected from glibenclamide, glipizide, gliclazide, **glimepiride**, tolazamide, tolbutamide, acetohexamide, carbutamide, chlorpropamide, glibomuride, gliquidone, glisentide, glisolamide, glisoxepide, glyclopyamide, glycylamide and glipentide.

13. A method according to claim 10 or 11, wherein the insulin sensitiser is (+)-5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]**methyl**]-2,4-thiazolidinedione (or troglitazone), 5-[4-[(1-methylcyclohexyl)methoxy]**benzyl**] **thiazolidine**-2,4-dione (or ciglitazone), 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]**benzyl**]**thiazolidine**-2,4-dione (or pioglitazone) or 5-[(2-**benzyl**-2,3-dihydrobenzopyran)-5-ylmethyl)**thiazolidine**-2,4-dione (or englitazone);) or a derivative thereof.

L3 ANSWER 7 OF 15 USPATFULL on STN
AN 2002:266346 USPATFULL
TI Treatment of **diabetes** with thiazolidinedione and sulphonylurea
IN Smith, Stephen Alistair, Bramfield, UNITED KINGDOM
PA SmithKline Beecham p.l.c. (non-U.S. corporation)
PI US 2002147226 A1 20021010
AI US 2002-103326 A1 20020321 (10)
RLI Continuation of Ser. No. US 2001-848511, filed on 2 May 2001, ABANDONED
Continuation of Ser. No. US 1999-445859, filed on 15 Dec 1999, ABANDONED
A 371 of International Ser. No. WO 1998-EP3688, filed on 15 Jun 1998, UNKNOWN
PRAI GB 1997-12854 19970618
GB 1998-6710 19980327
DT Utility
FS APPLICATION
LREP SMITHKLINE BEECHAM CORPORATION, CORPORATE INTELLECTUAL PROPERTY-US, UW2220, P. O. BOX 1539, KING OF PRUSSIA, PA, 19406-0939
CLMN Number of Claims: 21
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 464
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method for the treatment of **diabetes** mellitus and conditions associated with **diabetes** mellitus in a mammal, which method comprises administering an effective non-toxic and pharmaceutically acceptable amount of an insulin sensitiser and an insulin secretagogue, to a mammal in need thereof.
TI Treatment of **diabetes** with thiazolidinedione and sulphonylurea
AB A method for the treatment of **diabetes** mellitus and conditions associated with **diabetes** mellitus in a mammal, which method comprises administering an effective non-toxic and pharmaceutically acceptable amount of an insulin sensitiser and. . .
SUMM [0001] This invention relates to a method of treatment, in particular to a method for the treatment of **diabetes** mellitus, especially non-insulin dependent **diabetes** (NIDDM) or Type II **diabetes** and conditions associated with **diabetes**

mellitus.

SUMM . . . of insulin secretagogues. The suiphonylureas act as hypoglycaemic agents and are used in the treatment of NIDDM (or Type II **diabetes**). Examples of sulphonylureas include glibenclamide, glipizide, gliclazide, **glimepiride**, tolazamide and tolbutamide.

SUMM . . . relates to certain thiazolidinedione derivatives disclosed as having antihyperglycaemic and antihyperlipidaemic activity. One particular thiazolidinedione disclosed in EP 0306228 is 5-[4-[2-(N-**methyl**-N-(2-**pyridyl**)amino)ethoxy]**benzyl**] **thiazolidine**-2,4-dione (hereinafter `Compound (I)`). WO94/05659 discloses certain salts of Compound (I) including the maleate salt at example 1 thereof.

SUMM . . . insulin secretagogue provides a particularly beneficial effect on glycaemic control such combination is therefore particularly useful for the treatment of **diabetes** mellitus, especially Type II **diabetes** and conditions associated with **diabetes** mellitus. The treatment is also indicated to proceed with minimum side effects.

SUMM [0011] Accordingly, the invention provides a method for the treatment of **diabetes** mellitus, especially Type II **diabetes** and conditions associated with **diabetes** mellitus in a mammal such as a human, which method comprises administering an effective non-toxic and pharmaceutically acceptable amount of. . .

SUMM . . . insulin sensitiser, such as Compound (I), together with an insulin secretagogue for use in a method for the treatment of **diabetes** mellitus, especially Type II **diabetes** and conditions associated with **diabetes** mellitus.

SUMM . . . such as Compound (I), and an insulin secretagogue for use in the manufacture of a composition for the treatment of **diabetes** mellitus, especially Type II **diabetes** and conditions associated with **diabetes** mellitus.

SUMM [0017] Suitable sulphonylureas include glibenclamide, glipizide, gliclazide, **glimepiride**, tolazamide and tolbutamide.

SUMM [0021] Other suitable thiazolidinedione insulin sensitisers include (+)-5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]**methyl**]-2,4-thiazolidinedione (or troglitazone), 5-[4-[(1-methylcyclohexyl)methoxy]**benzyl**] **thiazolidine**-2,4-dione (or ciglitazone), 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]**benzyl**]**thiazolidine**-2,4-dione (or pioglitazone) or 5-[(2-**benzyl**-2,3-dihydrobenzopyran)-5-ylmethyl)**thiazolidine**-2,4-dione (or englitazone).

SUMM [0022] In one particular aspect, the method comprises the administration of 2 to **12 mg** of Compound (I), especially when administered per day.

SUMM [0023] Particularly, the method comprises the administration of 2 to 4, 4 to 8 or 8 to **12 mg** of Compound (I) per day.

SUMM [0026] Particularly, the method comprises the administration of 8 to **12 mg** of Compound (I), especially when administered per day.

SUMM [0037] When used herein the term `conditions associated with **diabetes**` includes those conditions associated with **diabetes** mellitus itself and complications associated with **diabetes** mellitus.

SUMM [0038] `Conditions associated with **diabetes** mellitus itself` include hyperglycaemia, insulin resistance, including acquired insulin resistance and obesity. Further conditions associated with **diabetes** mellitus itself include hypertension and cardiovascular disease, especially atherosclerosis and conditions associated with insulin resistance. Conditions associated with insulin resistance include polycystic ovarian syndrome and steroid induced insulin resistance and gestational **diabetes**.

SUMM [0039] `Complications associated with **diabetes** mellitus` includes renal disease, especially renal disease associated with Type II **diabetes**, neuropathy and retinopathy.

SUMM [0040] Renal diseases associated with Type II **diabetes** include nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal disease.

SUMM [0043] **Diabetes** mellitus is preferably Type II **diabetes**.

SUMM . . . aspect the present invention also provides a pharmaceutical composition comprising an insulin sensitiser, such as Compound (I) especially 2 to **12 mg** thereof, an insulin secretagogue and a pharmaceutically acceptable carrier therefor.

SUMM [0050] Such compositions may be prepared by admixing an insulin sensitiser, such as Compound (I) especially 2 to **12 mg** thereof, the insulin secretagogue and a pharmaceutically acceptable carrier therefor.

SUMM . . . dosages of the Compound of formula (I) comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or **12 mg** of Compound (I).

SUMM . . . other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, **methyl** cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous. . . almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example **methyl** or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

SUMM [0069] The present invention also provides a pharmaceutical composition comprising an insulin sensitiser, such as Compound (I) especially 2 to **12 mg** thereof, an insulin secretagogue and a pharmaceutically acceptable carrier therefor, for use as an active therapeutic substance.

SUMM . . . In particular, the present invention provides a pharmaceutical composition comprising an insulin sensitiser, such as Compound (I) especially 2 to **12 mg** thereof, an insulin secretagogue and a pharmaceutically acceptable carrier therefor, for use in the treatment of **diabetes** mellitus, especially Type II **diabetes** and conditions associated with **diabetes** mellitus.

SUMM [0073] A range of 8 to **12 mg** includes a range of 8.1 to 12, 8.2 to 12, 8.3 to 12, 8.4 to 12, 8.5 to 12, 8.6. . . to 12, 8.7 to 12, 8.8 to 12, 8.9 to 12, 9 to 12, 10 to 12 or 11 to **12 mg**.

CLM What is claimed is:

1. A method for the treatment of **diabetes** mellitus and conditions associated with **diabetes** mellitus in a mammal, which method comprises administering an effective non-toxic and pharmaceutically acceptable amount of an insulin sensitiser and. . .

3. A method according to claim 1, wherein the insulin secretagogue is glibenclamide, glipizide, gliclazide, **glimepiride**, tolazamide or tolbutamide.

4. A method according to any one of claims 1 to 3, wherein the insulin sensitiser is 5-[4-[2-(N-**methyl**-N-(2-**pyridyl**)amino)ethoxy]**benzyl**]**thiazolidine**-2,4-dione (Compound I).

5. A method according to any one of claims 1 to 4, which comprises the administration of 2 to **12 mg** of Compound (I).

. . . one of claims 1 to 5, which comprises the administration of 2 to 4, 4

to 8 or 8 to **12 mg** of Compound (I).

9. A method according to any one of claims 1 to 6, which comprises the administration of 8 to **12 mg** of Compound (I).

13. A method according to claim 1, wherein the insulin sensitiser is (+)-5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]**methyl**]-2,4-thiazolidinedione (or troglitazone), 5-[4-[(1-methylcyclohexyl)methoxy]**benzyl**] **thiazolidine**-2,4-dione (or ciglitazone), 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]**benzyl**]**thiazolidine**-2,4-dione (or pioglitazone) or 5-[(2-**benzyl**-2,3-dihydrobenzopyran)-5-ylmethyl)**thiazolidine**-2,4-dione (or englitazone); or a pharmaceutically acceptable form thereof.

16. A composition according to claim 14 or claim 15, wherein the insulin secretagogue is glibenclamide, glipizide, gliclazide, **glimepiride**, tolazamide or tolbutamide.

18. A composition according to any one of claims 14 to 17, which comprises 2 to **12 mg** of Compound (I).

. . . composition comprising an insulin sensitiser, an insulin secretagogue and a pharmaceutically acceptable carrier therefor, for use in the treatment of **diabetes** mellitus and conditions associated with **diabetes** mellitus.

21. A composition according to any one of claims 14, 20 or 21, wherein the insulin sensitiser is (+)-5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]**methyl**]-2,4-thiazolidinedione (or troglitazone), 5-[4-[(1-methylcyclohexyl)methoxy]**benzyl**]**thiazolidine** -2,4-dione (or ciglitazone), 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy] **benzyl**]**thiazolidine**-2,4-dione (or pioglitazone) or 5-[(2-**benzyl**-2,3-dihydrobenzopyran)-5-ylmethyl) **thiazolidine**-2,4-dione (or englitazone); or a pharmaceutically acceptable form thereof.

L3 ANSWER 8 OF 15 USPATFULL on STN
AN 2002:99423 USPATFULL
TI Treatment of **diabetes** with thiazolidinedione, insulin secretagogue and alpha glucocidase inhibitor
IN Buckingham, Robin Edwin, Welwyn Garden City, UNITED KINGDOM
Smith, Stephen Alistair, Bramfield, UNITED KINGDOM
PA SmithKline Beecham plc (non-U.S. corporation)
PI US 2002052324 A1 20020502
AI US 2001-989572 A1 20011120 (9)
RLI Continuation of Ser. No. US 1999-445908, filed on 15 Dec 1999, PENDING A 371 of International Ser. No. WO 1998-GB2112, filed on 16 Jul 1998, UNKNOWN
PRAI GB 1997-15298 19970718
DT Utility
FS APPLICATION
LREP GLAXOSMITHKLINE, Corporate Intellectual Property - UW2220, P.O. Box 1539, King of Prussia, PA, 19406-0939
CLMN Number of Claims: 22
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 487
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method for the treatment of **diabetes** mellitus and conditions

associated with **diabetes** mellitus in a mammal, which method comprises administering an effective non-toxic and pharmaceutically acceptable amount of an insulin sensitizer, an insulin secretagogue and an alpha glucosidase inhibitor antihyperglycaemic agent, to a mammal in need thereof; and composition for use in such method.

TI Treatment of **diabetes** with thiazolidinedione, insulin secretagogue and alpha glucocidase inhibitor

AB A method for the treatment of **diabetes** mellitus and conditions associated with **diabetes** mellitus in a mammal, which method comprises administering an effective non-toxic and pharmaceutically acceptable amount of an insulin sensitizer, an. . .

SUMM [0001] This invention relates to a method of treatment, in particular to a method for the treatment of **diabetes** mellitus, especially non-insulin dependent **diabetes** (NIDDM) or Type 2 **diabetes** and conditions associated with **diabetes** mellitus.

SUMM . . . known examples of insulin secretagogues. The sulphonylureas act as antihyperglycaemic agents and are used in the treatment of Type 2 **diabetes**. Examples of sulphonylureas include glibenclamide, glipizide, gliclazide, **glimepiride**, tolazamide and tolbutamide.

SUMM . . . Alpha glucosidase inhibitor antihyperglycaemic agents, such as acarbose, emiglitate and miglitol, are commonly used in the treatment of Type 2 **diabetes**.

SUMM . . . relates to certain thiazolidinedione derivatives disclosed as having antihyperglycaemic and antihyperlipidaemic activity. One particular thiazolidinedione disclosed in EP 0306228 is 5-[4-[2-(N-**methyl**-N-(2-**pyridyl**)amino)ethoxy]**benzyl**] **thiazolidine**-2,4-dione (hereinafter `Compound (I)`). WO94/05659 discloses certain salts of Compound (I) including the maleate salt.

SUMM . . . by Reference. provides a particularly beneficial effect on glycaemic control, such combination is therefore particularly useful for the treatment of **diabetes** mellitus. especially Type 2 **diabetes**, and conditions associated with **diabetes** mellitus. The treatment is also indicated to proceed with minimum side effects.

DETD [0011] Accordingly, the invention provides a method for the treatment of **diabetes** mellitus, especially Type 2 **diabetes** and conditions associated with **diabetes** mellitus, in a mammal such as a human, which method comprises administering an effective non-toxic and pharmaceutically acceptable amount of. . .

DETD . . . an insulin secretagogue and an alpha glucosidase inhibitor antihyperglycaemic agent, in the manufacture of a composition for the treatment of **diabetes** mellitus, especially Type 2 **diabetes** and conditions associated with **diabetes** mellitus.

DETD [0017] Other suitable thiazolidinedione insulin sensitisers include (+)-5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]**methyl**]-2,4-thiazolidinedione (or troglitazone), 5-[4-[(1-methylcyclohexyl)methoxy]**benzyl**] **thiazolidine**-2,4-dione (or ciglitazone), 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]**benzyl**]**thiazolidine**-2,4-dione (or pioglitazone) or 5-[(2-**benzyl**-2,3-dihydrobenzopyran)-5-ylmethyl)**thiazolidine**-2,4-dione (or englitazone)

DETD [0019] Suitable sulphonylureas include glibenclamide, glipizide, gliclazide, **glimepiride**, tolazamide and tolbutamide.

DETD [0024] In one particular aspect, the method comprises the administration of 2 to **12 mg** of Compound (I), especially when administered per day.

DETD [0025] Particularly, the method comprises the administration of 2 to 4, 4 to 8 or 8 to **12 mg** of Compound (I) per day.

DETD [0028] Particularly, the method comprises the administration of 8 to

12 mg of Compound (I), especially when administered per day.

DETD [0039] When used herein the term `conditions associated with **diabetes**` includes conditions associated with **diabetes** mellitus itself and complications associated with **diabetes** mellitus. Also included in `conditions associated with **diabetes** ` are those conditions associated with the pre-diabetic state.

DETD [0041] `Conditions associated with **diabetes** mellitus itself` include hyperglycaemia, insulin resistance, including acquired insulin resistance. Further conditions associated with **diabetes** mellitus itself include hypertension and cardiovascular disease, especially atherosclerosis and conditions associated with insulin resistance. Conditions associated with insulin resistance include polycystic ovarian syndrome and steroid induced insulin resistance and gestational **diabetes**.

DETD [0042] `Complications associated with **diabetes** mellitus` includes renal disease, specially renal disease associated with Type 2 **diabetes**, neuropathy and retinopathy.

DETD [0043] Renal diseases associated with Type 2 **diabetes** include nephropathy, glomerulonephritis, glomerular sclerosis, hypertensive nephrosclerosis and end stage renal disease. Additional renal diseases associated with Type 2 **diabetes** include nephrotic syndrome.

DETD [0045] **Diabetes** mellitus is preferably Type 2 **diabetes** .

DETD . . . the present invention also provides a pharmaceutical composition comprising an insulin sensitiser, such as Compound (I) and especially 2 to **12 mg** thereof, an insulin secretagogue and an alpha glucosidase inhibitor antihyperglycaemic agent and a pharmaceutically acceptable carrier therefor.

DETD [0056] Such compositions may be prepared by admixing an insulin sensitiser, such as Compound (I) and especially 2 to **12 mg** thereof, an insulin secretagogue and an alpha glucosidase inhibitor antihyperglycaemic agent and a pharmaceutically acceptable carrier therefor.

DETD . . . dosages, including unit dosages. of Compound (I) comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or **12 mg** of Compound (I).

DETD . . . other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, **methyl** cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats: emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous. . . almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example **methyl** or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

DETD . . . The present invention also provides a pharmaceutical composition comprising an insulin sensitiser, such as Compound (I) and especially 2 to **12 mg** thereof, an insulin secretagogue and an alpha glucosidase inhibitor antihyperglycaemic agent and a pharmaceutically acceptable carrier therefor, for use as. . .

DETD [0077] The invention also provides the use of an insulin sensitiser, such as Compound (I) and especially 2 to **12 mg** thereof, an insulin secretagogue and an alpha glucosidase inhibitor antihyperglycaemic agent for the manufacture of a medicament for the treatment of **diabetes** mellitus and conditions associated with **diabetes** mellitus.

DETD . . . particular, the present invention provides a pharmaceutical composition comprising an insulin sensitiser, such as Compound (I) and especially 2 to **12 mg** thereof, an insulin secretagogue and an alpha glucosidase inhibitor antihyperglycaemic agent

and a pharmaceutically acceptable carrier therefor, for use in the treatment of **diabetes** mellitus and conditions associated with **diabetes** mellitus.

DETD [0081] A range of 8 to **12 mg** includes a range of 8.1 to 12, 8.2 to 12, 8.3 to 12, 8.4 to 12, 8.5 to 12, 8.6. . . to 12. 8.7 to 12, 8.8 to 12, 8.9 to 12, 9 to 12, 10 to 12 or 11 to **12 mg**.

CLM What is claimed is:

1. A method for the treatment of **diabetes** mellitus and conditions associated with **diabetes** mellitus in a mammal, which method comprises administering an effective non-toxic and pharmaceutically acceptable amount of an insulin sensitiser, an. . .

2. A method according to claim 1, wherein the insulin secretagogue is glibenclamide, glipizide, gliclazide, **glimepiride**, tolazamide, tolbutamide, acetohexamide, carbutamide, chlorpropamide, glibomuride, gliquidone, glisentide, glisolamide, glisoxepide, glyclopyamide, glycylamide or repaglinide.

4. A method according to any one of claims 1 to 3, wherein the insulin sensitiser is 5-[4-.about.2-(N-**methyl**-N-(2-**pyridyl**)amino)ethoxy]**benzyl**]**thiazolidine**-2,4-dione (Compound I).

5. A method according to any one of claims 1 to 4, which comprises the administration of 2 to **12 mg** of Compound (I).

. . . one of claims 1 to 5, which comprises the administration of 2 to 4, 4 to 8 or 8 to **12 mg** of Compound (I).

9. A method according to any one of claims 1 to 6, which comprises the administration of 8 to **12 mg** of Compound (I).

13. A method according to claim 1, wherein the insulin sensitiser is (+)-5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]**methyl**]-2,4-thiazolidinedione (or troglitazone), 5-[4-[(1-methylcyclohexyl)methoxy]**benzyl**]**thiazolidine**-2,4-dione (or ciglitazone), 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]**benzyl**]**thiazolidine**-2,4-dione (or pioglitazone) or 5-[(2-**benzyl**-2,3-dihydrobenzopyran)-5-ylmethyl)**thiazolidine**-2,4-dione (or englitazone); or a pharmaceutically acceptable form thereof.

16. A composition according to claim 14 or claim 15, wherein the insulin secretagogue is glibenclamide, glipizide, gliclazide, **glimepiride**, tolazamide or tolbutamide, acetohexamide, carbutamide, chlorpropamide, glibomuride, gliquidone, glisentide, glisolamide, glisoxepide, glyclopyamide, glycylamide or repaglinide.

19. A composition according to any one of claims 14 to 17, which comprises 2 to **12 mg** of Compound (I).

. . . insulin secretagogue, an alpha glucosidase inhibitor antihyperglycaemic agent and a pharmaceutically acceptable carrier therefor, for use in the treatment of **diabetes** mellitus and conditions associated with **diabetes** mellitus.

22. A composition according to any one of claim 14, 20 or 21, wherein the insulin sensitiser is (+)-5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]**methyl**]-2,4-thiazolidinedione (or troglitazone), 5-[4-[(1-methylcyclohexyl)methoxy]**benzyl**]**thiazolidine**-2,4-dione (or ciglitazone), 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]

benzyl]thiazolidine-2,4-dione (or pioglitazone) or 5-[(2-**benzyl**-2,3-dihydrobenzopyran)-5-ylmethyl) **thiazolidine**-2,4-dione (or englitazone); or a pharmaceutically acceptable form thereof.

L3 ANSWER 9 OF 15 USPATFULL on STN
AN 2002:85604 USPATFULL
TI Treatment of **diabetes** with thiazolidinedione and sulphonylurea
IN Buckingham, Robin Edwin, Welwyn Garden City, UNITED KINGDOM
Smith, Stephen Alistair, Bramfield, UNITED KINGDOM
PA SmithKline Beecham p.l.c. (non-U.S. corporation)
PI US 2002045649 A1 20020418
AI US 2001-975883 A1 20011012 (9)
RLI Continuation of Ser. No. US 1999-445907, filed on 15 Dec 1999, UNKNOWN
PRAI GB 1997-15306 19970718
DT Utility
FS APPLICATION
LREP GLAXOSMITHKLINE, Corporate Intellectual Property - UW2220, P.O. Box 1539, King of Prussia, PA, 19406-0939
CLMN Number of Claims: 21
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 482
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method for the treatment of **diabetes** mellitus and conditions associated with **diabetes** mellitus in a mammal, which method comprises administering an effective non-toxic and pharmaceutically acceptable amount of an insulin sensitiser and a sub-maximal amount of an insulin secretagogue, to a mammal in need thereof; and a pharmaceutical composition for use in such method.
TI Treatment of **diabetes** with thiazolidinedione and sulphonylurea
AB A method for the treatment of **diabetes** mellitus and conditions associated with **diabetes** mellitus in a mammal, which method comprises administering an effective non-toxic and pharmaceutically acceptable amount of an insulin sensitiser and. . .
SUMM [0001] This invention relates to a method of treatment, in particular to a method for the treatment of **diabetes** mellitus, especially non-insulin dependent **diabetes** (NIDDM) (or Type 2 **diabetes**) and conditions associated with **diabetes** mellitus.
SUMM . . . known examples of insulin secretagogues. The sulphonylureas act as hypoglycaemic agents and are used in the treatment of Type 2 **diabetes**. Examples of sulphonylureas include glibenclamide, glipizide, gliclazide, **glimepiride**, tolazamide and tolbutamide.
SUMM . . . relates to certain thiazolidinedione derivatives disclosed as having hypoglycaemic and hypolipidaemic activity. One particular thiazolidinedione disclosed in EP 0306228 is 5-[4-[2-(N-**methyl**-N-(2-**pyridyl**)amino)ethoxy]**benzyl**] **thiazolidine**-2,4-dione (hereinafter `Compound (I)`). WO94/05659 discloses certain salts of Compound (I) including the maleate salt.
SUMM . . . insulin secretagogue provides a particularly beneficial effect on glycaemic control, such combination is therefore particularly useful for the treatment of **diabetes** mellitus and conditions associated with **diabetes**. Lowering the dose of the insulin secretagogue in the presence of a full dose of insulin sensitising agent also has. . .
SUMM [0010] Accordingly, the invention provides a method for the treatment of **diabetes** mellitus, especially Type 2 **Diabetes**, and conditions associated with **diabetes** in a mammal such as a human, which method comprises administering an effective non-toxic and

pharmaceutically acceptable amount of an. . .

SUMM . . . Compound (I), together with a sub-maximal amount of an insulin secretagogue for use in a method for the treatment of **diabetes** mellitus, especially Type 2 **diabetes** and conditions associated with **diabetes** mellitus.

SUMM . . . Compound (I), and a sub-maximal amount of an insulin secretagogue in the manufacture of a composition for the treatment of **diabetes** mellitus, especially Type 2 **diabetes** and conditions associated with **diabetes** mellitus.

SUMM . . . with an insulin secretagogue for use in reducing the likelihood, frequency and/or severity of hypoglycaemic episodes in the treatment of **diabetes** mellitus, especially Type 2 **diabetes** and conditions associated with **diabetes** mellitus, wherein the dose of the insulin secretagogue is a sub-maximal dose.

SUMM . . . for the manufacture of a composition for reducing the likelihood, frequency and/or severity of hypoglycaemic episodes in the treatment of **diabetes** mellitus, especially Type 2 **diabetes** and conditions associated with **diabetes** mellitus, wherein the amount of the insulin secretagogue is sub-maximal.

SUMM [0020] Other suitable thiazolidinedione insulin sensitisers include (+)-5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]**methyl**]-2,4-thiazolidinedione (or troglitazone), 5-[4-[(1-methylcyclohexyl)methoxy]**benzyl**] **thiazolidine**-2,4-dione (or ciglitazone), 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]**benzyl**]**thiazolidine**-2,4-dione (or pioglitazone) or 5-[(2-**benzyl**-2,3-dihydrobenzopyran)-5-ylmethyl)**thiazolidine**-2,4-dione (or englitazone).

SUMM [0022] Suitable sulphonylureas include glibenclamide, glipizide, gliclazide, **glimepiride**, tolazamide and tolbutamide.

SUMM [0025] In one particular aspect, the method comprises the administration of 2 to **12 mg** of Compound (I), especially when administered per day.

SUMM [0026] Particularly, the method comprises the administration of 2 to 4, 4 to 8 or 8 to **12 mg** of Compound (I) per day.

SUMM [0029] Particularly, the method comprises the administration of 8 to **12 mg** of Compound (I), especially when administered per day.

SUMM [0041] When used herein the term `conditions associated with **diabetes**` includes those conditions associated with **diabetes** mellitus itself and complications associated with **diabetes** mellitus.

SUMM [0042] `Conditions associated with **diabetes** mellitus itself` include hyperglycaemia, insulin resistance, including acquired insulin resistance. Further conditions associated with **diabetes** mellitus itself include hypertension and cardiovascular disease, especially atherosclerosis and conditions associated with insulin resistance. Conditions associated with insulin resistance include polycystic ovarian syndrome and steroid induced insulin resistance and gestational **diabetes**.

SUMM [0043] `Complications associated with **diabetes** mellitus` includes renal disease, especially renal disease associated with Type 2 **diabetes**, neuropathy and retinopathy.

SUMM [0044] Renal diseases associated with Type 2 **diabetes** include nephropathy, glomerulonephritis, glomerular sclerosis, hypertensive nephroscierosis and end stage renal disease. Additional renal diseases associated with Type 2 **diabetes** include nephrotic syndrome.

SUMM [0047] **Diabetes** mellitus is preferably Type 2 **diabetes**

.

SUMM . . . insulin sensitiser is administered at its normal, appropriate dose, for example Compound (I) is administered at a dose selected from 2-**12 mg** per day, for example 1, 2, 4 or 8 mg per

day.

SUMM . . . the present invention also provides a pharmaceutical composition comprising an insulin sensitiser, such as Compound (I) and especially 2 to **12 mg** thereof, a sub-maximal amount of an insulin secretagogue and a pharmaceutically acceptable carrier therefor.

SUMM [0053] Such compositions may be prepared by admixing an insulin sensitiser, such as Compound (I) and especially 2 to **12 mg** thereof, a sub-maximal amount of an insulin secretagogue and a pharmaceutically acceptable carrier therefor.

SUMM . . . dosages, including unit dosages, of Compound (I) comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or **12 mg** of Compound (I).

SUMM . . . other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, **methyl** cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats: emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous. . . almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example **methyl** or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

SUMM . . . The present invention also provides a pharmaceutical composition comprising an insulin sensitiser, such as Compound (I) and especially 2 to **12 mg** thereof, a sub-maximal amount of an insulin secretagogue and a pharmaceutically acceptable carrier therefor, for use as an active therapeutic. . .

SUMM [0070] The invention also provides the use of an insulin sensitiser, such as Compound (I) and especially 2 to **12 mg** thereof, a sub-maximal amount of an insulin secretagogue for the manufacture of a medicament for the treatment of **diabetes** mellitus and conditions associated with **diabetes**.

DETD . . . particular, the present invention provides a pharmaceutical composition comprising an insulin sensitiser, such as Compound (I) and especially 2 to **12 mg** thereof, a sub-maximal amount of an insulin secretagogue and a pharmaceutically acceptable carrier therefor, for use in the treatment of **diabetes** and conditions associated with **diabetes**.

DETD [0074] A range of 8 to **12 mg** includes a range of 8.1 to 12, 8.2 to 12, 8.3 to 12, 8.4 to 12, 8.5 to 12, 8.6. . . to 12, 8.7 to 12, 8.8 to 12, 8.9 to 12, 9 to 12, 10 to 12 or 11 to **12 mg**.

CLM What is claimed is:

1. A method for the treatment of **diabetes** mellitus and conditions associated with **diabetes** mellitus in a mammal, which method comprises administering an effective non-toxic and pharmaceutically acceptable amount of an insulin sensitiser and. . .

3. A method according to claim 1, wherein the insulin secretagogue is glibenclamide, glipizide, gliclazide, **glimepiride**, tolazamide, tolbutamide, acetohexamide, carbutamide, chlorpropamide, glibornuride, gliquidone, glisentide, glisolamide, glisoxepide, glyclopyamide and glycylamide or repaglinide.

4. A method according to any one of claims 1 to 3, wherein the insulin sensitiser is 5-[4-[2-(N-**methyl**-N-(2-**pyridyl**)amino)ethoxy]**benzyl**]**thiazolidine**-2,4-dione (Compound I) or a tautomeric form thereof and/or a pharmaceutically acceptable derivative thereof.

5. A method according to any one of claims 1 to 4, which comprises the administration of 2 to **12 mg** of Compound (I).

. . . one of claims 1 to 5, which comprises the administration of 2 to 4, 4 to 8 or 8 to **12 mg** of Compound (I).

9. A method according to any one of claims 1 to 6, which comprises the administration of 8 to **12 mg** of Compound (I).

13. A method according to claim 1, wherein the insulin sensitiser is (+)-5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]**methyl**]-2,4-thiazolidinedione (or troglitazone), 5-[4-[(1-methylcyclohexyl)methoxy]**benzyl**]**thiazolidine**-2,4-dione (or ciglitazone), 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]**benzyl**]**thiazolidine**-2,4-dione (or pioglitazone) or 5-[(2-**benzyl**-2,3-dihydrobenzopyran)-5-ylmethyl)**thiazolidine**-2,4-dione (or englitazone); or a tautomeric form thereof and/or a pharmaceutically acceptable derivative thereof.

16. A composition according to claim 14 or claim 15, wherein the insulin secretagogue is glibenclamide, glipizide, gliclazide, **glimepiride**, tolazamide or tolbutamide, acetohexamide, carbutamide, chlorpropamide, glibornuride, gliquidone, glisentide, glisolamide, glisoxepide, glyclopyamide and glycylamide or repaglinide.

18. A composition according to any one of claims 14 to 17, which comprises 2 to **12 mg** of Compound (I).

. . . sensitiser, a sub-maximal amount of an insulin secretagogue and a pharmaceutically acceptable carrier therefor, for use in the treatment of **diabetes** mellitus and conditions associated with **diabetes** mellitus.

21. A composition according to any one of claims 14, 19 or 20, wherein the insulin sensitiser is (+)-5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]**methyl**]-2,4-thiazolidinedione (or troglitazone), 5-[4-[(1-methylcyclohexyl)methoxy]**benzyl**]**thiazolidine**-2,4-dione (or ciglitazone), 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]**benzyl**]**thiazolidine**-2,4-dione (or pioglitazone) or 5-[(2-**benzyl**-2,3-dihydrobenzopyran)-5-ylmethyl)**thiazolidine**-2,4-dione (or englitazone); or a tautomeric form thereof and/or a pharmaceutically acceptable derivative thereof.

L3 ANSWER 10 OF 15 USPATFULL on STN
AN 2002:48618 USPATFULL
TI Substituted N-(indole-2-carbonyl-) amides and derivatives as glycogen phosphorylase inhibitors
IN Hoover, Dennis J., Stonington, CT, UNITED STATES
Hulin, Bernard, Essex, CT, UNITED STATES
Martin, William H., Essex, CT, UNITED STATES
Treadway, Judith L., Gales Ferry, CT, UNITED STATES
PI US 2002028810 A1 20020307
AI US 2001-881136 A1 20010614 (9)
RLI Division of Ser. No. US 1997-952668, filed on 2 Dec 1997, GRANTED, Pat. No. US 6297269 A 371 of International Ser. No. WO 1995-IB443, filed on 6 Jun 1995, UNKNOWN
DT Utility
FS APPLICATION
LREP Gregg C. Benson, Pfizer Inc., Patent Department, MS 4159,, Eastern Point Road, Groton, CT, 06340
CLMN Number of Claims: 38
ECL Exemplary Claim: 1

DRWN No Drawings
LN.CNT 4097
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention relates to certain indole-2-carboxamides of formula (I) and the pharmaceutically acceptable salts and prodrugs thereof, wherein R.sub.6 is carboxy, (C.sub.1-C.sub.8)alkoxycarbonyl, C(O)NR.sub.8R.sub.9 or C(O)R.sub.12, useful as inhibitors of glycogen phosphorylase, methods of treating glycogen phosphorylase dependent diseases or conditions with such compounds and pharmaceutical compositions comprising such compounds.

SUMM . . . This invention relates to glycogen phosphorylase inhibitors, pharmaceutical compositions containing such inhibitors and the use of such inhibitors to treat **diabetes**, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemias, hyperlipidemia, atherosclerosis and myocardial ischemia in mammals.

SUMM [0002] In spite of the early discovery of insulin and its subsequent widespread use in the treatment of **diabetes**, and the later discovery of and use of sulfonylureas (e.g. Chlorpropamide.TM. (Pfizer), Tolbutamide.TM. (Upjohn), Acetohexamide.TM. (E.I. Lilly), Tolazamide.TM. (Upjohn)) and biguanides (e.g. Phenformin.TM. (Ciba Geigy), Mefformin.TM. (G. D. Searle)) as oral hypoglycemic agents, the treatment of **diabetes** remains less than satisfactory. The use of insulin, necessary in about 10% of diabetic patients in which synthetic hypoglycemic agents are not effective (Type I **diabetes**, insulin dependent **diabetes** mellitus), requires multiple daily doses, usually by self injection. Determination of the proper dosage of insulin requires frequent estimations of. . . causes hypoglycemia, with effects ranging from mild abnormalities in blood glucose to coma, or even death. Treatment of non-insulin dependent **diabetes** mellitus (Type II **diabetes**, NIDDM) usually consists of a combination of diet, exercise, oral agents, e.g. sulfonylureas, and in more severe cases, insulin. However,. . .

SUMM . . . whom the causative agent or disorder is unknown. While such "essential" hypertension is often associated with disorders such as obesity, **diabetes** and hypertriglyceridemia, the relationship between these disorders has not been elucidated. Additionally, many patients display the symptoms of high blood. . .

SUMM [0016] This invention is directed to glycogen phosphorylase inhibitor compounds of Formula I useful for the treatment of **diabetes**, hyperglycemia, hypercholesterolemia, hypertension, hypennsulinemia, hyperlipidemia, atherosclerosis and myocardial ischemia.

SUMM [0023] R.sub.4 is H, **methyl**, ethyl, n-propyl, hydroxy(C.sub.1-C.sub.3)alkyl, (C.sub.1-C.sub.3)alkoxy(C.sub.1-C.sub.3)alkyl, phenyl(C.sub.1-C.sub.4)alkyl, phenylhydroxy(C.sub.1-C.sub.4)alkyl, phenyl(C.sub.1-C.sub.4)alkoxy(C.sub.1-C.sub.4)alkyl, thien-2- or 3-yl(C.sub.1-C.sub.4)alkyl or fur-2- or -3-yl(C.sub.1-C.sub.4)alkyl wherein said R.sub.4 rings are mono-,. . .

SUMM [0030] R.sub.9 is H, (C.sub.1-C.sub.8)alkyl, hydroxy, (C.sub.1-C.sub.8)alkoxy, methylene-perfluorinated(C.sub.1-C.sub.8)alkyl, phenyl, **pyridyl**, thienyl, furyl, pyrrolyl, pyrrolidinyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, pyranyl, piperidinyl, morpholinyl, pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl or. . .

SUMM [0032] R.sub.9 is mono- or di-substituted (C.sub.1-C.sub.5)alkyl, wherein said substituents are independently phenyl, **pyridyl**, furyl, pyrrolyl, pyrrolidinyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, pyranyl, pyridinyl, piperidinyl, morpholinyl, pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl or. . .

SUMM [0033] wherein the nonaromatic nitrogen-containing R.sub.9 rings are optionally mono-substituted on nitrogen with (C.sub.1-C.sub.6)alkyl, **benzyl**, benzoyl or (C.sub.1-C.sub.6)alkoxycarbonyl and wherein

the R.sub.9 rings are optionally mono-substituted on carbon with halo, (C.sub.1-C.sub.4)alkyl, (C.sub.1-C.sub.4)alkoxy, hydroxy, amino, or. .

SUMM [0036] with the proviso that if R.sub.4 is H, **methyl**, ethyl or n-propyl R.sub.5 is OH;

SUMM [0037] with the proviso that if R.sub.5 and R.sub.7 are H, then R.sub.4 is not H, **methyl**, ethyl, n-propyl, hydroxy(C.sub.1-C.sub.3)alkyl or (C.sub.1-C.sub.3)alkoxy(C.sub.1-C.sub.3)alkyl and R, is C(O)NR.sub.8R.sub.9, C(O)R.sub.12 or (C.sub.1-C.sub.4)alkoxycarbonyl.

SUMM [0039] R.sub.1 is 5-H, 5-halo, 5-**methyl** or 5-cyano;

SUMM [0054] R.sub.9 is H, (C.sub.1-C.sub.8)alkyl, hydroxy, hydroxy(C.sub.1-C.sub.6)alkyl, (C.sub.1-C.sub.8)alkoxy, **pyridyl**, morpholinyl, piperazinyl, pyrrolidinyl, piperidinyl, imidazolyl or thiazolyl or (C.sub.1-C.sub.4)alkyl mono-substituted with **pyridyl**, morpholinyl, piperazinyl, pyrrolidinyl, piperidinyl, imidazolyl or thiazolyl.

SUMM [0056] 5-Chloro-1H-indole-2-carboxylic acid [(1S)-((R)-hydroxy-dimethylcarbamoyl-**methyl**)-2-phenyl-ethyl]-amide,

SUMM [0057] 5,6-Dichloro-1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(methoxy-**methyl**-carbamoyl)-**methyl**]-2-phenyl-ethyl}-amide,

SUMM [0058] 5-Chloro-1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(methoxy-**methyl**-carbamoyl)-**methyl**]-2-phenyl-ethyl}-amide,

SUMM [0059] 5-Chloro-1H-indole-2-carboxylic acid ((1S)-{(R)-hydroxy-[(2-hydroxy-ethyl)-**methyl**-carbamoyl]-**methyl**}-2-phenyl-ethyl)-amide,

SUMM [0060] 5-Chloro-1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(**methyl**-pynidin-2-yl-carbamoyl)-**methyl**]-2-phenyl-ethyl}-amide or

SUMM [0061] 5-Chloro-1H-indole-2-carboxylic acid ((1S)-{(R)-hydroxy-[**methyl**-(2-pyridin-2-yl-ethyl)-carbamoyl]-**methyl**}-2-phenyl-ethyl)-amide.

SUMM [0066] R.sub.4 is **benzyl**;

SUMM [0067] R.sub.8 is **methyl**; and

SUMM [0068] R.sub.9 is **methyl**;

SUMM [0073] R.sub.4 is **benzyl**;

SUMM [0074] R.sub.8 is **methyl**; and

SUMM [0079] R.sub.4 is **benzyl**;

SUMM [0080] R.sub.8 is **methyl**; and

SUMM [0085] R.sub.4 is **benzyl**;

SUMM [0086] R.sub.8 is **methyl**; and

SUMM [0091] R.sub.4 is **benzyl**;

SUMM [0092] R.sub.8 is **methyl**; and

SUMM [0097] R.sub.4 is **benzyl**;

SUMM [0098] R.sub.8 is **methyl**; and

SUMM [0106] 5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-(2R)-hydroxy-3-(4-**methyl**-piperazin-1-yl)-3-oxo-propyl]-amide hydrochloride,

SUMM [0107] 5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-(2R)-hydroxy-3-(3-hydroxy-azetidin-1-yl)-3-oxo-propyl]-amide,

SUMM [0108] 5-Chloro-1H-indole-2-carboxylic acid ((1S)-**benzyl**-(2R)-hydroxy-3-isoxazolidin-2-yl-3-oxo-propyl)-amide,

SUMM [0109] 5-Chloro-1H-indole-2-carboxylic acid ((1S)-**benzyl**-(2R)-hydroxy-3-[1,2]-oxazinan-2-yl-3-oxo-propyl)-amide,

SUMM [0110] 5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-(2R)-hydroxy-3-((3S)-hydroxy-pyrrolidin-1-yl)-3-oxo-propyl]-amide,

SUMM [0111] 5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-3-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)-hydroxy-3-oxo-propyl]-amide,

SUMM [0112] 5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-3-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)-hydroxy-3-oxo-propyl]-amide or

SUMM [0113] 5-Chloro-1H-indole-2-carboxylic acid ((1S)-**benzyl**

-(2R)-hydroxy-3-morpholin-4-yl-3-oxo-propyl)-amide.

SUMM [0118] R.sub.4 is **benzyl**; and

SUMM [0123] R.sub.4 is **benzyl**; and

SUMM [0128] R.sub.4 is **benzyl**; and

SUMM [0133] R.sub.4 is **benzyl**; and

SUMM [0138] R.sub.4 is **benzyl**; and

SUMM [0143] R.sub.4 is **benzyl**; and

SUMM [0148] R.sub.4 is **benzyl**; and

SUMM [0153] R.sub.4 is **benzyl**; and

SUMM [0156] R.sub.1 is H. halo, **methyl** or cyano;

SUMM [0175] R.sub.4 is **benzyl**.

SUMM [0177] R.sub.1 is H, halo, **methyl** or cyano;

SUMM [0187] R.sub.1 is H, halo, **methyl** or cyano;

SUMM [0198] Yet another aspect of this invention is directed to a method for treating **diabetes** in a mammal by administering to a mammal suffering from **diabetes** a **diabetes** treating amount of a Formula I compound.

SUMM . . . to a mammal suffering from hypercholesterolemia a hypercholesterolemia treating amount of a Formula I compound. Included in the treatment of **diabetes** is the prevention or attenuation of long term complications such as neuropathy, nephropathy, retinopathy or cataracts.

SUMM [0208] Another aspect of this invention is directed to pharmaceutical compositions for the treatment of **diabetes** which comprise a therapeutically effective amount of a glycogen phosphorylase inhibitor;

SUMM . . . insulin analogs (e.g. LysPro insulin); GLP-1 (7-37) (insulinotropin) and GLP-1 (7-36)-NH.sub.2; Sulfonylureas and Analogs: chlorpropamide, glibenclamide, tolbutamide, tolazamide, acetohexamide, glypizide.RTM., **glimepiride**, repaglinide, meglitinide; Biguanides: metformin, phenformin, buformin; .alpha.2-Antagonists and Imidazolines: midaglizole, isaglidole, deriglidole, idazoxan, efaroxan, fluparoxan; Other insulin secretagogues: linogliride, A-4166;. . .

SUMM [0212] Another aspect of this invention is a method of treating **diabetes** in a mammal with the above described combination compositions.

SUMM . . . glycogen molecule, These disorders are ameliorated by reduction of or characterized by an elevation of glycogen phosphorylase activity. Examples include **diabetes**, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis and myocardial ischemia.

SUMM . . . straight chain or branched saturated hydrocarbon. Exemplary of such alkyl groups (assuming the designated length encompasses the particular example) are **methyl**, ethyl, propyl, isopropyl, butyl, sec-butyl, tertiary butyl, pentyl, isopentyl, hexyl and isohexyl.

SUMM . . . such as (but not limited to) sodium, potassium, calcium, magnesium, ammonium or protonated benzathine (N,N'-dibenzylethylenediamine), choline, ethanolamine, diethanolamine, ethylenediamine, meglamine (N-**methyl**-glucamine), benethamine (N-benzylphenethylamine), piperazine or tromethamine (2-amino-2-hydroxymethyl-1,3-propanediol).

SUMM . . . R.sub.12 contains carboxy) wherein the free hydrogen is replaced by (C.sub.1-C.sub.4)alkyl, (C.sub.2-C.sub.12)alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-**methyl** -1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 8 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-**methyl**-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to. . .

SUMM . . . of Formula I wherein the free hydrogen of the hydroxy substituent (e.g., R.sub.5 is hydroxy) is replaced by (C.sub.1-C.sub.6)alkanoyloxymethyl, 1-((C.sub.1-

C.sub.6)alkanoyloxy)ethyl, 1-**methyl**-1-((C.sub.1-C.sub.6)alkanoyloxy)ethyl, (C.sub.1-C.sub.6)alkoxycarbonyloxymethyl, N-(C.sub.1-C.sub.6)alkoxycarbonylaminomethyl, succinoyl, (C.sub.1-C.sub.6)alkanoyl, .alpha.-amino(C.sub.1-C.sub.4)alkanoyl, arylactyl and .alpha.-aminoacyl, or .alpha.-aminoacyl-.alpha.-aminoacyl wherein said .alpha.-aminoacyl moieties are independently any of the naturally. . .

SUMM . . . is a free hydrogen which is replaced by R-carbonyl, RO-carbonyl, NRR'-carbonyl where R and R' are each independently ((C.sub.1-C.sub.10)alkyl, (C.sub.3-C.sub.7)cycloalkyl, **benzyl**, or R-carbonyl is a natural .alpha.-aminoacyl or natural .alpha.-aminoacyl-natural .alpha.-aminoacyl, --C(OH)C(O)OY wherein (Y is H, (C.sub.1-C.sub.6)alkyl or **benzyl**), --(OY.sub.0)Y.sub.1 wherein Y.sub.0 is (C.sub.1-C.sub.4) alkyl and Y.sub.1 is ((C.sub.1-C.sub.6)alkyl, carboxy(C.sub.1-C.sub.6)alkyl, amino(C.sub.1-C.sub.4)alkyl or mono-N- or di-N,N-(C.sub.1-C.sub.6)alkylaminoalkyl, --C(Y.sub.2)Y.sub.3 wherein Y.sub.2 is H or **methyl** and Y.sub.3 is mono-N- or di-N,N-(C.sub.1-C.sub.6)alkylamino, morpholino, piperidin-1-yl or pyrrolidin-1-yl.

SUMM . . . those protecting groups commonly used in peptide synthesis (such as N-t-butoxycarbonyl, N-carbobenzyloxy, and 9-fluorenylmethylenoxycarbonyl for amines and lower alkyl or **benzyl** esters for carboxylic acids) which are not chemically reactive under the coupling conditions described above (and immediately preceding the Examples. . .

SUMM [0247] Alternatively, the Formula VIIIA indole 2-carboxylic acid may be prepared by condensation of a Formula IX ortho **methyl** nitro compound with an oxalate ester to yield the Formula X indole ester followed by reduction of the nitro group. . .

SUMM . . . R.sub.6 is C(O)R.sub.12 or C(O)NR.sub.8R.sub.9. An example of the conversion of a Formula XXI cyanohydrin to the corresponding Formula XXII **methyl** ester with removal of the t-boc protecting group is provided in PCT publication WO/9325574, Example 1a. Other examples wherein a. . .

SUMM [0256] For example, the preparation of the Formula XXI compound wherein P.sub.T is Boc, R.sub.3 is H, R.sub.4 is **benzyl** and the stereochemistry of carbons a and b is (S) and (R) respectively, employing this route together with purification by. . .

SUMM . . . group (P.sub.T) (such as Boc). The protected compound is esterified with an alcohol and converted to an ester, preferably the **methyl** or ethyl ester of the Formula XXXI compound. This may be accomplished by treating the Formula XXX compound with **methyl** or ethyl iodide in the presence of a suitable base (e.g., K.sub.2CO.sub.3) in a polar solvent such as dimethylformamide. The. . .

SUMM . . . Benoiton, Can. J. Chem 1977, 55, 906-910, and Hansen, J. Org. Chem. 1985, 50 945-950. For example, when R.sub.3 is **methyl**, sodium hydride and **methyl** iodide in tetrahydrofuran are utilized. Deprotection of the Formula XLI compound yields the desired Formula XXX compound.

SUMM . . . acid may be N-alkylated by a three-step sequence involving reductive benzylation (such as with benzaldehyde, Pd/C-catalyzed hydrogenation) to give the mono-N-**benzyl** derivative and reductive amination with the appropriate acyl compound (for example with formaldehyde and sodium cyanoborohydride to introduce R.sub.3 as **methyl**) to give the N-**Benzyl**, N-R.sub.3-substituted amino acid. The N-**benzyl** protecting group is conveniently removed (for example by hydrogenation with an appropriate catalyst) to yield the Formula XXX compound. Specific. . .

SUMM . . . reductive amination conditions, to give R.sub.8R.sub.9N(P.sub.T). The protecting group (P.sub.T) iS removed (e.g. by exhaustive catalytic hydrogenation when P.sub.T is

benzyl) to give a compound of formula R.sub.8R.sub.9NH. Appropriate reductive amination conditions are available from the literature to one skilled in. . .

SUMM [0284] N-(1-hydroxyalkyl) amides, N-(1-hydroxy-1-(alkoxycarbonyl) **methyl**) amides or compounds where R.sub.2 has been replaced by C(OH)C(O)OY may be prepared by the reaction of the parent amide. . .

SUMM . . . beads are then washed once with the same buffer prior to blocking with 50 mM HEPES and 1 M glycine **methyl** ester at pH 8.0 for one hour at room temperature. Blocking buffer is removed and replaced with 50 mM HEPES. . .

SUMM . . . group assignment, animals are dosed orally each day for four days with the vehicle consisting of either: 1) 0.25% w/v **methyl** cellulose in water without pH adjustment; or 2) 0.1% Pluronic.RTM. P105 Block Copolymer Surfactant (BASF Corporation, Parsippany, N.J.) in 0.1%. . . with the test compound or the vehicle alone. All drugs are administered in vehicle consisting of either: 1) 0.25% w/v **methyl** cellulose in water without pH adjustment; or 2) 10% DMSO/0.1% Pluronic.RTM. P105 (BASF Corporation, Parsippany, N.J.) in 0.1% saline without. . .

DETD 5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl** -(2R)-hydroxy-3-(4-**methyl**-piperazin-1-yl)-3-oxo-propyl]-amide hydrochloride

DETD [0347] (3S)-Amino-(2R)-hydroxy-1-(4-**methyl**-piperazin-1-yl)-4-phenyl-butan-1-one dihydrochloride (0.25 mmol) and 5-chloro-1H-indole-2-carboxylic acid (0.30 mmol) were coupled according to Procedure A and the product purified by chromatography. . .

DETD (3S)-Amino-(2R)-hydroxy-1-(4-**methyl**-piperazin-1-yl)-4-phenyl-butan-1-one dihydrochloride

DETD [0349] [(1S)-**Benzyl**-(2R)-hydroxy-3-(4-**methyl** -piperazin-1-yl)-3-oxo-propyl]-carbamic acid tert-butyl ester (0.190 g, 0.5 mmol) was dissolved in 4 M HCl-dioxane at 25.degree. C. for 0.5 hours. The. . .

DETD [(1S)-**Benzyl**-(2R)-hydroxy-3-(4-**methyl** -piperazin-1-yl)-3-oxo-propyl]-carbamic acid tert-butyl ester

DETD 5-Chloro-1H-indole-2-carboxylic acid [(1S)-((R)-hydroxy-methylcarbamoyl-**methyl**)-2-phenyl-ethyl]-amide

DETD (3S)-[(5-Fluoro-1H-indole-2-carbonyl)-amino]-(2R)-hydroxy-4-phenyl-butyric acid **methyl** ester

DETD [0354] (3S)-Amino-(2R)-hydroxy-4-phenyl-butyric acid **methyl** ester (0.8 mmol, WO 9325574 Example 1A) and 54luoro-1H-indole-2-carboxylic acid (0.8 mmol) were coupled according to Procedure A (except at. . .

DETD (3S)-[(5-Bromo-1H-indole-2-carbonyl)-amino]-(2R)-hydroxy-4-phenyl-butyric acid **methyl** ester

DETD [0357] (3S)-Amino-(2R)-hydroxy-4-phenyl-butyric acid **methyl** ester (WO 93/25574, Example 1A) (0.7 mmol) and 5-bromo-1H-indole-2-carboxylic acid (0.7 mmol) were coupled according to Procedure A (except at. . .

DETD 5-Fluoro-1H-indole-2-carboxylic acid [(1S)-((R)-dimethylcarbamoyl-hydroxy-**methyl**)-2-phenyl-ethyl]-amide

DETD 5-Bromo-1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(methoxy-**methyl**-carbamoyl)-**methyl**]-2-phenyl-ethyl}-amide

DETD [0361] (3S)-Amino-(2R)-hydroxy-N-methoxy-N-**methyl** -4-phenyl-butyramide hydrochloride (0.36 mmol) and 3-[(5-bromo-1H-indole-2-carbonyl)-amino]-2-hydroxy-4-phenyl-butyric acid (0.36 mmol) were coupled according to Procedure A and the crude product purified by. . .

DETD 5-Chloro-3-**methyl**-1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(methoxy-**methyl**-carbamoyl)-**methyl**]-2-phenyl-ethyl}-amide

DETD [0362] (3S)-Amino-(2R)-hydroxy-N-methoxy-N-**methyl** -4-phenyl-butyramide hydrochloride (0.3 mmol) and 5-chloro-3-

methyl-1H-indole-2-carboxylic acid (0.3 mmol) were coupled according to Procedure A and the crude product purified by trituration with ether: Yield, 59%,. . .

DETD 5-Chloro-3-**methyl**-1H-indole-2-carboxylic acid

DETD [0364] 2N NaOH (20 mL) was added to a suspension of 5-chloro-3-**methyl**-1H-indole-2-carboxylic acid ethyl ester (7.0 g, 29.4 mmol) in methanol (50 mL) and the resulting mixture stirred at 25.degree. C. for. . .

DETD 5-Chloro-3-**methyl**-1H-indole-2-carboxylic acid ethyl ester

DETD (3S)-Amino-(2R)-hydroxy-N-methoxy-N-**methyl**-4-phenyl-butyramide hydrochloride 31055-274-2 31055-85-1

DETD [0366] {(1S)-[(R)-Hydroxy-(methoxy-**methyl**-carbamoyl)-**methyl**]-2-phenyl-ethyl}-carbamic acid tert-butyl ester (791 mg, 2.3 mmol) was dissolved in 4M HCl-dioxanes for 45 minutes at 25.degree. C. for 45. . .

DETD {(1S)-[(R)-Hydroxy-(methoxy-**methyl**-carbamoyl)-**methyl**]-2-phenyl-ethyl}-carbamic acid tert-butyl ester

DETD (3S)-[(5,6-Dichloro-1H-indole-2-carbonyl)-amino]-(2R)-hydroxy-4-phenyl-butyric acid **methyl** ester

DETD [0368] (3S)-Amino-(2R)-hydroxy-4-phenyl-butyric acid **methyl** ester (1.2 mmol) and 5,6-dichloro-1H-indole-2-carboxylic acid (1.2 mmol) were coupled according to Procedure A (reaction time 72 hours) and the. . .

DETD . . . mL). The resulting solution was treated at 3.degree. C. with a solution of diethyl oxalate (10.0 g, 62 mmol) and 2-**methyl**-3,4-dichloro-1-nitrobenzene (10.0 g, 62 mmol) over 5-10 min, and the resulting solution stirred 30 minutes at 3.degree. C. and 25.degree. C.. . .

DETD 5-Cyano-1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(methoxy-**methyl**-carbamoyl)-**methyl**]-2-phenyl-ethyl}-amide

DETD [0372] (3S)-Amino-(2R)-hydroxy-N-methoxy-N-**methyl**-4-phenyl-butyramide hydrochloride (0.3 mmol) and 5cyano-1H-indole-2-carboxylic acid (0.3 mmol) were coupled according to Procedure A (reaction time 5 days). The crude. . .

DETD . . . 400 ml ethanol) was added at 0.degree. C. to a mixture of distilled diethyl oxalate (120 g, 821 mmol) and 3-**methyl**-4-nitrobenzonitrile (32 g, 197 mmol). The resulting red solution was heated at 40.degree. C. for 18 hours. The cooled mixture was. . .

DETD 5-**Methyl**-1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(methoxy-**methyl**-carbamoyl)-**methyl**]-2-phenyl-ethyl}-amide

DETD [0377] (3S)-Amino-(2R)-hydroxy-N-methoxy-N-**methyl**-4-phenyl-butyramide hydrochloride (0.5 mmol) and 5-**methyl**-1H-indole-2-carboxylic acid (0.5 mmol) were coupled according to Procedure A (reaction temperature 0-25.degree. C., extraction with acid first, then base) and. . .

DETD 5-Fluoro-1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(methoxy-**methyl**-carbamoyl)-**methyl**]-2-phenyl-ethyl}-amide

DETD [0380] (3S)-Amino-(2R)-hydroxy-N-methoxy-N-**methyl**-4-phenyl-butyramide hydrochloride (0.5 mmol) and 5-fluoro-1H-indole-2-carboxylic acid (0.5 mmol) were coupled according to Procedure A (washing first with acid then base). . .

DETD 1H-Indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(methoxy-**methyl**-carbamoyl)-**methyl**]-2-phenyl-ethyl}-amide

DETD [0382] (3S)-Amino-(2R)-hydroxy-N-methoxy-N-**methyl**-4-phenyl-butyramide hydrochloride (0.26 mmol) and 1H-indole-2-carboxylic acid (0.28 mmol) were coupled according to Procedure A (0-25.degree. C. reaction temperature) and the. . .

DETD 5-Chloro-1H-indole-2-carboxylic acid {(1S)-[(methoxy-**methyl**-carbamoyl)-**methyl**]-2-phenyl-ethyl}-amide

DETD [0386] 2N NaOH (3.0 mL) was added to a suspension of (3S)-[(5-chloro-1H-indole-2-carbonyl)-amino]-4-phenyl-butyric acid

methyl ester (1.28 g, 3.45 mmol) in methanol (10 mL) at 25.degree. C. After 18 hours the reaction mixture was diluted. . .

DETD (3S)-[(5-Chloro-1H-indole-2-carbonyl)-amino]-(2R)-hydroxy-4-phenylbutyric acid **methyl** ester

DETD [0387] 1-(3-dimethylaminopropyl)-3-ethylcarbodilmide hydrochloride (DEC, 71 g, 370 mmol) was added to a mixture of (3S)-amino-(2R)-hydroxy-4-phenyl-butyric acid **methyl** ester (WO 93/25574, Example 1A, 77.5 g, 370 mmol), 6-chloro-1H-indole-2-carboxylic acid (72.45 g, 370 mmol) and 1-hydroxybenzotriazole hydrate in dichloromethane. . .

DETD [0392] (RS)-3-amino-2-hydroxypropionic acid **methyl** ester hydrochloride (6.6 mmol) and 5-chloro-1H-indole-2-carboxylic acid (6.6 mmol) were coupled according to Procedure A (except that acid, then base. . .

DETD (RS)-3-amino-2-hydroxypropionic acid **methyl** ester hydrochloride

DETD 5-Chloro-1H-indole2-carboxylic acid [(1S)-((R)-methoxy-methylcarbamoyl-**methyl**)-2-phenyl-ethyl]-amide

DETD [0398] (1S,2R)-(1-**Benzyl**-2-dimethylcarbamoyl-2-methoxy-ethyl)-carbamic acid tert-butyl ester (283 mg, 0.84 mmol) was dissolved in 4N HCl-dioxane (1 mL) for 1.5 hours at 25.degree. C.,. . .

DETD (1S,2R)-(1-**Benzyl**-2-dimethylcarbamoyl-2-methoxy-ethyl)-carbamic acid tert-butyl ester

DETD [0399] Sodium hydride-oil dispersion (53 mg of 50%) was added to a solution of (1S,2R)-(1-**benzyl**-2-dimethylcarbamoyl-2-hydroxy-ethyl)-carbamic acid tert-butyl ester (322 mg, 1.0 mmol) in tetrahydrofuran (4 mL) at 0.degree. C. After effervescence ceased (several minutes), **methyl** iodide (155 mg) was added, and after 15 minutes another 11 mg NaH dispersion and 23 mg **methyl** iodide were added. After 15 more minutes aqueous ammonium chloride solution and ethyl acetate were added, and the organic layer. . .

DETD (1S,2R)-(1-**Benzyl**-2-dimethylcarbamoyl-2-hydroxy-ethyl)-carbamic acid tert-butyl ester

DETD 5-Chloro-1H-indole-2-carboxylic acid (3-azetidin-1-yl-(1S)-**benzyl**-(2R)-hydroxy-3-oxo-propyl)-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-(2R)-methoxy-2-(methoxy-**methyl**-carbamoyl)-ethyl]-amide

DETD [0402] (3S,2R)-3-Amino-(2R),N-dimethoxy-N-**methyl**-4-phenyl-butyramide (0.31 mmol) and 5-chloro-1H-indole-2-carboxylic acid (0.31 mmol) were coupled according to Procedure A and the product purified by chromatography on. . .

DETD (3S,2R)-3-Amino-(2R),N-dimethoxy-N-**methyl**-4-phenyl-butyramide

DETD [0405] (1S,2R)-(1-**Benzyl**-2-methoxy-**methyl**-carbamoyl-2-methoxy-ethyl)-carbamic acid tert-butyl ester (113 mg, 0.32 mmol) was dissolved in 4N HCl-dioxane (4 mL) at 25.degree. C. for 1 hour,. . .

DETD (1S,2R)-(1-**Benzyl**-2-methoxy-**methyl**-carbamoyl-2-methoxy-ethyl)-carbamic acid tert-butyl ester

DETD [0406] Sodium hydride dispersion (30 mg of 50% in oil) was added to a solution of (1S,2R)-(1-**Benzyl**-2-methoxy-**methyl**-carbamoyl-2-hydroxy-ethyl)-carbamic acid tert-butyl ester in tetrahydrofuran (2 mL) at 0.degree. C. After 5 minutes mrethyl iodide (175 mg) was added and. . .

DETD [(2S)-[(5-Chloro-1H-indole-2-carbonyl)-amino]-(1R)-(methoxy-**methyl**-carbamoyl)-3-phenyl-propoxy]-acetic acid **benzyl** ester

DETD [0407] (1R,2S)-[2-Amino-1-(methoxy-**methyl**-carbamoyl)-3-phenyl-propoxy]-acetic acid **benzyl** ester hydrochloride (162 mg, 0.38 mmol) was coupled with 5-chloro-1H-indole-2-carboxylic acid (71 mg, 0.36 mmol) according to Procedure A (0-25.degree.. . .

DETD (1R,2S)-[2-Amino-1-(methoxy-**methyl**-carbamoyl)-3-phenyl-propoxy]-acetic acid **benzyl** ester hydrochloride

DETD [0408] (1R,2S)-[2-tert-Butoxycarbonylamino-1-(methoxy-**methyl**

-carbamoyl)-3-phenyl-propoxy]-acetic acid **benzyl** ester (170 mg, 0.35 mmol) was dissolved in 4N HCl-dioxane (2 mL) for 1.5 hours at 25.degree. C., concentrated, the. . .

DETD (1R,2S)-[2-tert-Butoxycarbonylamino-1-(methoxy-**methyl**-carbamoyl)-3-phenyl-proooxyl-acetic acid **benzyl** ester

DETD [0409] Sodium hydride dispersion (120 mg of 50% in oil, 2.8 mmol) was added to a solution of (1S,2R)-(1-**benzyl**-2-methoxy-**methyl**-carbamoyl-2-hydroxy-ethyl)-carbamic acid tert-butyl ester (858 mg, 2.5 mmol) in tetrahydrofuran (8 mL) at 0.degree. C. After effervescence ceased **benzyl** bromoacetate (0.56 g, 2.5 mmol) was added and the mixture was brought to 25.degree. C. After 2 hours more NaH dispersion was added (**12 mg**), and the mixture was stirred 1 hour, diluted with ethyl acetate and saturated ammonium chloride, the organic layer separated, washed. . .

DETD [(2S)-[(5-Chloro-1H-indole-2-carbonyl)-amino]-(1R)-(methoxy-**methyl**-carbamoyl)-3-phenyl-propoxy]-acetic acid

DETD [0410] A mixture of [(2S)-[(5-chloro-1H-indole-2-carbonyl)-amino]-(1R)-(methoxy-**methyl**-carbamoyl)-3-phenyl-propoxy]-acefic acid **benzyl** ester (120 mg, 0.2 mmol) and 50% moist palladium hydroxide on carbon catalyst in methanol (50 mL) was shaken at. . . of a solid, HPLC (60/40) 4.81 (37%) and 6.24 minutes (63%). .sup.1H NMR and MS analysis showed these to be **methyl** esters of the 5-des-Cl and title product respectively. This solid was dissolved in THF and treated with 1N NaOH (170. . .

DETD [0414] [(1S)-((S)-Carbamoyl-hydroxy-**methyl**)-2-phenyl-ethyl]-carbamic acid tert-butyl ester (0.50 g, 1.7 mmol) was dissolved in 4 M HCl-dioxane at 25.degree. C. for 1 hour. The. . .

DETD [(1S)-((S)-Carbamoyl-hydroxy-**methyl**)-2-phenyl-ethyl]-carbamic acid tert-butyl ester

DETD [0415] Tetrabutylammonium fluoride (23 mL of 1M in tetrahydrofuran) was added to a solution of {(1S)-[(S)-(tert-butyl-dimethyl-silanyloxy)-carbamoyl-**methyl**]-2-phenyl-ethyl}-carbamic acid tert-butyl ester in tetrahydrofuran (6 mL) at 0.degree. C. After 30 minutes the mixture was diluted with ethyl acetate. . .

DETD {(1S)-[(S)-(tert-Butyl-dimethyl-silanyloxy)-carbamoyl-**methyl**]-2-phenyl-ethyl}-carbamic acid tert-butyl ester

DETD [0416] 30% hydrogen peroxide (7.2 mL, 64 mmol) was added over a period of 15 minutes to a solution of [1(S)-**benzyl**-(2S)-(tert-butyl-dimethyl-silanyloxy)-2-cyano-ethyl]-carbamic acid tert-butyl ester (Example 24D, 5.0 g, 12.8 mmol) and 1N NaOH (22 mL) in ethanol (110 mL) at 0.degree.. . .

DETD 5-Chloro-1H-indole-2-carboxylic acid {(1S)-[(S)-hydroxy-(methoxy-**methyl**-carbamoyl)-**methyl**]-2-phenyl-ethyl}-amide

DETD [0420] Aqueous 1N NaOH (2.6 mL) was added to a solution of (3S)-[(5-Chloro-1H-indole-2-carbonyl)amino]-(2S)-hydroxy-4-phenylbutyric acid **methyl** ester (500 mg, 1.29 mmol) in methanol at 25.degree. C. After 18 hours the mixture was concentrated, the residue dissolved. . .

DETD ((3S)-[(5-Chloro-1H-indole-2-carbonyl)-amino]-(2S)-hydroxy-4-phenyl-butyric acid **methyl** ester

DETD [0421] (3S)-Amino-(2S)-hydroxy-4-phenyl-butyric acid **methyl** ester (1.4 mmol) and 5-Chloro-1H-indole-2-carboxylic acid (1.37 mmol) were coupled according to Procedure A (0-25.degree. C. reaction, 40 hour reaction. . .

DETD (3S)-Amino-(2S)-hydroxy-4-phenyl-butyric acid **methyl** ester

DETD [0423] [1(S)-**Benzyl**-(2S)-(tert-butyl-dimethyl-silanyloxy)-2-cyano-ethyl]-carbamic acid tert-butyl ester (417 mg) was added to a solution of anhydrous HCl (3.2g) in methanol (20 mL) and the. . .

DETD [1(S)-**Benzyl**-(2S)-(tert-butyl-dimethyl-silanyloxy)-2-cyano-ethyl]-carbamic acid tert-butyl ester

DETD [0426] Aqueous 2N NaOH (375 mL) was added at 10-22.degree. C. to a solution of crude (3S)-[(5-chloro-1H-indole-2-carbonyl)-amino]-(2R)-

hydroxy-4-phenylbutyric acid **methyl** ester (containing 13% of the N,O-bis-5-chloro-1H-indole-2-carbonyl impurity, 140.7 g, 363 mmol) in methanol (1900 mL) and the mixture was allowed. . .

DETD [0429] A solution of (3S)-[(5-fluoro-1H-indole-2-carbonyl)-amino]-(2R)-hydroxy-4-phenyl-butyric acid **methyl** ester (190 mg, 0.5 mmol), 1N NaOH (1 mL) and methanol (5 mL) was stirred at 25.degree. C. for 18. . .

DETD [0430] Aqueous 1N NaOH (60 mL) was added to a solution of (3S)-[(5-bromo-1H-indole-2-carbonyl)-amino]-(2R)-hydroxy-4-phenyl-butyric acid **methyl** ester (2.45 g, 5.7 mmol) in methanol (60 mL) at 25.degree. C. After 2 hours the mixture was concentrated and. . .

DETD [0433] Aqueous 1N NaOH (1.18 mL) was added to a suspension of (3S)-[(5,6-dichloro-1H-indole-2-carbonyl)-amino]-(2R)-hydroxy-4-phenyl-butyric acid **methyl** ester (249 mg, 0.6 mmol) in methanol (5 mL) at 25.degree. C. After 18 hours the mixture was concentrated, the. . .

DETD [0435] Aqueous 1N NaOH (1.69 mL) was added to a suspension of (3R)-[(5-Chloro-1H-indole-2-carbonyl)-amino]-(2R)-hydroxy-4-phenyl-butyric acid **methyl** ester (326 mg, 0.8 mmol) in methanol at 25.degree. C. After 2.5 hours the mixture was concentrated (starting material found). . .

DETD (3R)-[(5-Chloro-1H-indole-2-carbonyl)-amino]-(2R)-hydroxy-4-phenyl-butyric acid **methyl** ester

DETD [0438] (2R,3R)-3-Amino-2-hydroxy-4-phenylbutyric acid **methyl** ester hydrochloride (239 mg, 1.0 mmol) and 5-chloro-1H-indole-2-carboxylic acid (200 mg, 1.05 mmol) were coupled according to Procedure A (0-25.degree.. . .

DETD (2R,3R)-3-Amino-2-hydroxy-4-phenylbutyric acid **methyl** ester Hydrochloride

DETD 5-Chloro-1H-indole-2-carboxylic acid [(2RS)-hydroxy-2-(methoxy-**methyl**-carbamoyl)-ethyl]-amide

DETD [0443] A large excess of anhydrous ammonia was introduced into a solution of (3S)-[(5-chloro-1H-indole2-carbonyl)-amino]-(2R)-hydroxy-4-phenylbutyric acid **methyl** ester (100 mg, 0.27 mmol) in methanol (10 mL) and the mixture was heated in a stainless steel Parr reactor. . .

DETD 5,6-Dichloro-1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(methoxy-**methyl**-carbamoyl)-**methyl**]-2-phenyl-ethyl}-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid [(1S)-((R)-hydroxy-dimethylcarbamoyl-**methyl**)-2-phenyl-ethyl]-amid

DETD 5-Chloro-1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(hydroxy-**methyl**-carbamoyl)-**methyl**]-2-phenyl-ethyl}-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid [(1S)-((R)-hydroxy-methoxycarbamoyl-**methyl**)-2-phenyl-ethyl]-amide

DETD 5Chloro-1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(methoxy-**methyl**-carbamoyl)-**methyl**]-2-phenyl-ethyl}-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid (2S)-[(5-chloro-1H-indole-2-carbonyl)-amino]-(1R)-(methoxy-**methyl**-carbamoyl)-3-phenyl-propyl ester

DETD [0457] (3S)-Amino-(2R)-hydroxy-N-methoxy-N-**methyl** -4-phenyl-butyramide hydrochloride (4.2 mmol) and 5-chloro-1H-indole-2-carboxylic acid (4.2 mmol) were coupled according to Procedure A. The mixture was purified by chromatography. . . silica eluting with 33-50% ethyl acetate-hexanes giving the title substance (100 mg) and the more polar major substance 5-chloro-1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(methoxy-**methyl**-carbamoyl)-**methyl**]-2-phenyl-ethyl}-amide (970 mg), plus a mixture of the two substances (159 mg, mostly more polar product). For the title substance: PBMS. .

DETD 5-Chloro-1H-indole-2-carboxylic acid ((1S)-**benzyl** -(2R)-hydroxy-3-oxo-3-pyrrolidin-1-yl-propyl)-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-(2R)-hydroxy-3-(3-hydroxy-azetidin-1-yl)-3-oxo-propyl]-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid ((1S)-**benzyl**-(2R)-hydroxy-3-isoxazolidin-2-yl-3-oxo-propyl)-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid [(1S)-((R)-diethylcarbamoyl-hydroxy-**methyl**)-2-phenyl-ethyl]-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid ((1S)-{(R)-hydroxy-[(2-hydroxy-ethyl)-**methyl**-carbamoyl]-**methyl**}-2-phenyl-ethyl)-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid ((1S)-**benzyl**-(2R)-hydroxy-3-oxo-3-piperidin-1-yl-propyl)-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid ((1S)-**benzyl**-2(R)-hydroxy-3-morpholin-4-yl-3-oxo-propyl)-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid ((1S)-**benzyl**-(2R)-hydroxy-3-[1,2]oxazinan-2-yl-3-oxo-propyl)-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-(2R)-hydroxy-3-((3S)-hydroxy-pyrrolidin-1-yl)-3-oxo-propyl]-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid [(1S)-((R)-tert-butoxycarbamoyl-hydroxy-**methyl**)-2-phenyl-ethyl]-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid ((1S)-**benzyl**-(2R)-hydroxy-3-oxo-3-thiazolidin-3-yl-propyl)-amide

DETD [0480] **Thiazolidine** (0.70 mmol) and (3S)-[(5-chloro-1H-indole-2-carbonyl)-amino]-(2R)-hydroxy-4-phenyl-butyric acid (0.67 mmol) were coupled according to Procedure A (1 :1-dichloromethane-dimethylformamide solvent) giving product which was. . .

DETD 5-Bromo-1H-indole-2-carboxylic acid [(1S)-((R)-dimethylcarbamoyl-hydroxy-**methyl**)-2-phenyl-ethyl]-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(pyridin-3-vicarbamoyl)-**methyl**]-2-phenyl-ethyl}-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(2,2,2-trifluoro-ethylcarbamoyl)-**methyl**]-2-phenyl-ethyl}-amide

DETD (S)-5-Chloro-1H-indole-2-carboxylic acid [1-(methoxy-**methyl**-carbamoanecarbonyl)-2-phenyl-ethyl]-amide

DETD [0487] 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (DEC, 790 mg, 4.12 mmol), dichloroacetic acid (136 mg, 1.06 mmol) and 5-chloro-1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(methoxy-**methyl**-carbamoyl)-**methyl**]-2-phenyl-ethyl}-amide (287 mg, 0.69 mmol) were added, in this order, to a solution of anhydrous dimethylsulfoxide (4 mL) and toluene (anhydrous,. . . .

DETD 5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-(2R)-hydroxy-3-(4-hydroxy-piperidin-1-yl)-3-oxo-propyl]-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-(2R)-hydroxy-3-((3R,S)-hydroxy-piperidin-1-yl)-3-oxo-propyl]-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-(2R)-hydroxy-3-((2R)-hydroxymethyl-pyrrolidin-1-yl)-3-oxo-1propyl]-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid ((1S)-{(R)-[(2-dimethylamino-ethyl)-**methyl**-carbamoyl]-hydroxy-**methyl**}-2-phenyl-ethyl)-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-3-((3R,4R)-dihydroxy-pyrrolidin-1-yl)-2-hydroxy-3-oxo-propyl]-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-3-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)-hydroxy-3-oxo-propyl]-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-3-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)-hydroxy-3-oxo-propyl]-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid ((1S)-**benzyl**-(2R)-hydroxy-3-oxo-3-thiomorpholin-4-yl-propyl]-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(**methyl**-pyridin-2-yl-carbamoyl)-**methyl**]-2-phenyl-ethyl}-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-3-(4-formyl-piperazin-1-yl)-(2R)-hydroxy-3-oxo-propyl]-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**

-(2R)-hydroxy-3-(4-hydroxymethyl-piperidin-1-yl)-3-oxo-propyl]-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid ((1S)-{(R)-hydroxy-[**methyl**-(2-pyridin-2-yl-ethyl)-carbamoyl]-**methyl**}-2-phenyl-ethyl)-amide

DETD [0515] **Methyl**-(2-pyridin-2-yl-ethyl)-amine (0.77 mmol) and (3S)-[(5-chloro-1H-indole-2-carbonyl)-amino]-(2R)-hydroxy-4-phenyl-butyric acid (0.70 mmol) were coupled according to Procedure A (dimethylformamide solvent) and the product purified by. . .

DETD 5-Chloro-1H-indole-2-carboxylic acid {(1R)-[(S)-hydroxy-(methoxy-**methyl**-carbamoyl)-**methyl**]-2-phenyl-ethyl}-amide

DETD [0521] 5-Chloro-1H-indole-2-carboxylic acid (0.25 mmol) and (2S,3R)-3-amino-2-hydroxy-N-methoxy-N-**methyl**-4-phenyl-butyramide hydrochloride (0.25 mmol) were coupled according to Procedure A (0-25.degree. C., acid then base wash). The crude product was dissolved. . .

DETD (2S,3R)-3-amino-2-hydroxy-N-methoxy-N-**methyl**-4-phenyl-butyramide hydrochloride

DETD [0524] {1 (R)-[Hydroxy-((S)-methoxy-**methyl**-carbamoyl)-**methyl**]-2-phenyl-ethyl}-carbamic acid (285 mg, 0.8 mmol) was dissolved in cold 4N HCl-dioxane and the resulting solution stirred for 1 hour at. . .

DETD {(1S)-[Hydroxy-((R)-methoxy-**methyl**-carbamoyl)-**methyl**]-2-phenyl-ethyl}-carbamic acid

DETD 5-Chloro-1H-indole-2-carboxylic acid {(1R)-[hydroxy-((R)-methoxy-**methyl**-carbamoyl)-**methyl**]-2-phenyl-ethyl}-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-(2R)-hydroxy-3-oxo-3-(1-oxo-1-thiazolidin-3-yl)-propyl]-amide

DETD [0529] m-Chloroperoxybenzoic acid (62 mg of 50%, 0.18 mmol) was added at 25.degree. C. to a solution of 5-chloro-1H-indole-2-carboxylic acid ((1S)-**benzyl**-(2R)-hydroxy-3-oxo-3-thiazolidin-3-yl-propyl)-amide (80 mg, 0.18 mmol) in dichloromethane (2 mL). After 1 hour the mixture was poured into a mixture of saturated. . .

DETD 5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-(2R)-hydroxy-3-oxo-3-(1-oxo-1-thiomorpholinyl)-propyl]-amide (Example 70)

DETD 5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-3-(1,1-dioxo-1-thiomorpholin-4-yl)-(2R)-hydroxy-3-oxo-propyl]-amide (Example 71)

DETD [0530] m-Chloroperoxybenzoic acid (45 mg of 50%, 0.13 mmol) was added at 25.degree. C. to a solution of 5-chloro-1H-indole-2-carboxylic acid ((1S)-**benzyl**-(2R)-hydroxy-3-oxo-3-thiomorpholinyl-4-propyl)-amide (60 mg, 0.13 mmol) in dichloromethane (1.5 mL). After 1 hour the mixture was poured into a mixture of saturated. . .

DETD 5-Chloro-1H-indole-2-carboxylic acid [(1S)-((R)-hydroxy-hydroxycarbamoyl-**methyl**)-2-phenyl-ethyl]-amide

DETD [0534] Trifluoroacetic acid (2 mL) was added to a solution of 5chloro-1H-indole-2-carboxylic acid [(1S)-((R)-tert-butoxycarbamoyl-hydroxy-**methyl**)-2-phenyl-ethyl]-amide (256 mg, 0.58 mmol) in dichloromethane (2 mL) and the resulting solution was stirred for 18 hours at 25.degree. C.. . .

DETD 5-Chloro-1H-indole-2-carboxylic acid ((1S)-{[(**benzyl**-piperidin-4-yl)-**methyl**-carbamoyl]-(R)-hydroxy-**methyl**}-2-phenyl-ethyl)-amide

DETD [0536] (3S)-[(5-Chloro-1H-indole-2-carbonyl)amino]-(2R)-hydroxyphenylbutyric acid (310 mg, 0.8 mmol) and (1-**benzyl**-piperidin-4-yl)-**methyl**-amine hydrochloride (EPO publication 0 457 686, example 1A therein, 200 mg, 0.8 mmol) were coupled according to Procedure A (dimethylformamide. . .

DETD 4-({(3S)-[(5-Chloro-1H-indole-2-carbonyl)-amino]-(2R)-hydroxy-4-phenyl-butyryl}-**methyl**-amino)-piperidine-1-carboxylic acid tert-butyl ester

DETD 5-Chloro-1H-indole-2-carboxylic acid {(1-S)[(R)-hydroxy-(**methyl**

-piperidin-4-yl-carbamoyl)-**methyl**]-2-phenyl-ethyl}-amide hydrochloride

DETD [0540] 4-({(3S)-[(5-Chloro-1H-indole-2-carbonyl)-amino]-(2R)-hydroxy-4-phenyl-butyryl}-**methyl**-amino)-piperidine-1-carboxylic acid tert-butyl ester (292 mg, 0.5 mmol) was dissolved in 4M HCl-dioxane at 0.degree. C. and stirred for 1 hour. . .

DETD 5-Chloro-1H-indole-2-carboxylic acid ((1S)-{(R)-hydroxy-[**methyl**-(1-**methyl**-piperidin-4-yl)-carbamoyl]-**methyl**}-2-phenyl-ethyl)-amide hydrochloride

DETD . . . aqueous formaldehyde (37 weight % in water, 22 mg, 0.3 mmol) were added sequentially to a solution of 5-chloro-1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(**methyl**-piperidin-4-yl-carbamoyl)-**methyl**]-2-phenyl-ethyl}-amide hydrochloride (100 mg, 0.2 mmol) in methanol (2 mL) at 25.degree. C. After 18 hours the reaction mixture was filtered. . .

DETD (3S)-[(6-Chloro-1H-indol-2-carbonyl)-amino]-4-phenyl-butyric acid **methyl** ester

DETD [0544] (3S)-3-Amino-4-phenyl-butyric acid **methyl** ester hydrochloride (1.15 g, 5 mmol) and 5-chloro-1H-indole-2-carboxylic acid were coupled according to procedure A. The product was purified by. . .

DETD (3S)-Amino4-phenyl-butyric acid **methyl** ester hydrochloride

DETD [0545] (3S)-tert-Butoxycarbonylamino4-phenyl-butyric acid **methyl** ester (ref. Heterocycles, p. 1835 (1989) and J. Med. Chem. 1975, p. 761, 3.49 g, 12.1 mmol) was dissolved in. . .

CLM What is claimed is:

. . . or 7-nitro, cyano, (C.sub.1-C.sub.4)alkyl, (C.sub.1-C.sub.4)alkoxy, fluoromethyl, difluoromethyl or trifluoromethyl; R.sub.2 is H; R.sub.3 is H or (C.sub.1-C.sub.5)alkyl; R.sub.4 is H, **methyl**, ethyl, n-propyl, hydroxy(C.sub.1-C.sub.3)alkyl, (C.sub.1-C.sub.3)alkoxy(C.sub.1-C.sub.3)alkyl, phenyl(C.sub.1-C.sub.4)alkyl, phenylhydroxy(C.sub.1-C.sub.4)alkyl, phenyl(C.sub.1-C.sub.4)alkoxy(C.sub.1-C.sub.4)alkyl, thien-2- or -3-yl(C.sub.1-C.sub.4)alkyl or fur-2- or -3-yl(C.sub.1-C.sub.4)alkyl wherein said R.sub.4 rings are mono-,. . . C(O)NR.sub.8R.sub.9 or C(O)R.sub.12, wherein R.sub.8 is H, (C.sub.1-C.sub.3)alkyl, hydroxy or (C.sub.1-C.sub.3)alkoxy; and R.sub.9 is H, (C.sub.1-C.sub.8)alkyl, hydroxy, (C.sub.1-C.sub.8)alkoxy, methylene-perfluorinated(C.sub.1-C.sub.8)alkyl, phenyl, **pyridyl**, thienyl, furyl, pyrrolyl, pyrrolidinyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, pyranyl, piperidinyl, morpholinyl, pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl or. . . independently H, hydroxy, amino, mono-N- or di-N,N-(C.sub.1-C.sub.5)alkylamino; or R.sub.9 is mono- or di-substituted (C.sub.1-C.sub.5)alkyl, wherein said substituents are independently phenyl, **pyridyl**, furyl, pyrrolyl, pyrrolidinyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, pyranyl, pyridinyl, piperidinyl, morpholinyl, pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl or 1,3,5-triazinyl wherein the nonaromatic nitrogen-containing R.sub.9 rings are optionally mono-substituted on nitrogen with (C.sub.1-C.sub.6)alkyl, **benzyl**, benzoyl or (C.sub.1-C.sub.6)alkoxycarbonyl and wherein the R.sub.9 rings are optionally mono-substituted on carbon with halo, (C.sub.1-C.sub.4)alkyl, (C.sub.1-C.sub.4)alkoxy, hydroxy, amino, or. . . (C.sub.1-C.sub.5)alkoxy, carboxy, carbamoyl, mono-N- or di-N,N-(C.sub.1-C.sub.4)alkylcarbamoyl, (C.sub.1-C.sub.4)alkoxyimino, (C.sub.1-C.sub.4)alkoxymethoxy, (C.sub.1-C.sub.6)alkoxycarbonyl, carboxy(C.sub.1-C.sub.5)alkyl or hydroxy(C.sub.1-C.sub.5)alkyl; with the proviso that if R.sub.4 is H, **methyl**, ethyl or n-propyl, R.sub.5 is OH; with the proviso that if R.sub.5 and R.sub.7 are H, then R.sub.4 is not H, **methyl**, ethyl, n-propyl, hydroxy(C.sub.1-C.sub.3)alkyl or (C.sub.1-C.sub.3)alkoxy(C.sub.1-

C.sub.3)alkyl and R.sub.6 is C(O)NR.sub.8R.sub.9, C(O)R.sub.12 or (C.sub.1-C.sub.4)alkoxycarbonyl.

2. A compound as recited in claim 1 wherein R.sub.1 is 5-H, 5-halo, 5-**methyl**, 5-trifluoromethyl or 5-cyano; R.sub.10 and R.sub.11 are each independently H or halo; A is --C(H).dbd.; R.sub.2 and R.sub.3 are H;. . .
. H or fluoro; R.sub.6 is C(O)NR.sub.8R.sub.9; R.sub.8 is (C.sub.1-C.sub.3)alkyl, hydroxy or (C.sub.1-C.sub.3)alkoxy; and R.sub.9 is H, (C.sub.1-C.sub.8)alkyl, hydroxy, hydroxy(C.sub.1-C.sub.8)alkyl, (C.sub.1-C.sub.8)alkoxy, **pyridyl**, morpholinyl, piperazinyl, pyrrolidinyl, piperidinyl, imidazolyl or thiazolyl or (C.sub.1-C.sub.4)alkyl mono-substituted with **pyridyl**, morpholinyl, piperazinyl, pyrrolidinyl, piperidinyl, imidazolyl or thiazolyl.

4. A compound as recited in claim 3 selected from 5-Chloro-1H-indole-2-carboxylic acid [(1S)-((R)-hydroxy-dimethylcarbamoyl-**methyl**)-2-phenyl-ethyl]-amide, 5,6-Dichloro-1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(methoxy-**methyl**-carbamoyl)-**methyl**]-2-phenyl-ethyl}-amide, 5-Chloro-1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(methoxy-**methyl**-carbamoyl)-**methyl**]-2-phenyl-ethyl}-amide, 5-Chloro-1H-indole-2-carboxylic acid ((1S)-{(R)-hydroxy-[(2-hydroxy-ethyl)-**methyl**-carbamoyl]-**methyl**}-2-phenyl-ethyl)-amide, 5-Chloro-1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(**methyl**-pyridin-2-yl-carbamoyl)-**methyl**]-2-phenyl-ethyl}-amide or 5-Chloro-1H-indole-2-carboxylic acid ((1S)-{(R)-hydroxy-[**methyl**-(2-pyridin-2-yl-ethyl)-carbamoyl]-**methyl**}-2-phenyl-ethyl)-amide.

5. The compound as recited in claim 3 wherein R.sub.1 is 5-chloro; R.sub.10 and R.sub.11 are H; R.sub.4 is **benzyl**; R.sub.8 is **methyl**; and R.sub.9 is **methyl**.

6. The compound as recited in claim 3 wherein R.sub.1 is 5-chloro; R.sub.11 is H; R.sub.10 is 6-chloro; R.sub.4 is **benzyl**; R.sub.8 is **methyl**; and R.sub.9 is methoxy.

7. The compound as recited in claim 3 wherein R.sub.1 is 5-chloro; R.sub.10 and R.sub.11 are H; R.sub.4 is **benzyl**; R.sub.8 is **methyl**; and R.sub.9 is methoxy.

8. The compound as recited in claim 3 wherein R.sub.1 is 5-chloro; R.sub.10 and R.sub.11 are H; R.sub.4 is **benzyl**; R.sub.8 is **methyl**; and R.sub.9 is 2-(hydroxy)ethyl.

9. The compound as recited in claim 3 wherein R.sub.1 is 5-chloro; R.sub.10 and R.sub.11 are H; R.sub.4 is **benzyl**; R.sub.8 is **methyl**; and R.sub.9 is pyridin-2-yl.

10. The compound as recited in claim 3 wherein R.sub.1 is 5-chloro; R.sub.10 and R.sub.11 are H; R.sub.4 is **benzyl**; R.sub.8 is **methyl**; and R.sub.9 is 2-(pyridin-2-yl)ethyl.

12. A compound as recited in claim 1 selected from 5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-(2R)-hydroxy-3-(4-**methyl**-piperazin-1-yl)-3-oxo-propyl]-amide hydrochloride, 5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-(2R)-hydroxy-3-(3hydroxy-azetidin-1-yl)-3-oxo-propyl]-amide, 5-Chloro-1H-indole-2-carboxylic acid ((1S)-**benzyl**-(2R)-hydroxy-3-isoxazolidin-2-yl-3-oxo-propyl)-amide, 5-Chloro-1H-indole-2-carboxylic acid ((1S)-**benzyl**

-(2R)-hydroxy-3-[1,2]oxazinan-2-yl-3-oxo-propyl)-amide,
5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**
-(2R)-hydroxy-3-((3S)-hydroxy-pyrrolidin-1-yl)-3-oxo-propyl]-amide,
5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**
-3-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)-hydroxy-3-oxo-propyl]-amide,
5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**
-3-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)-hydroxy-3-oxo-propyl]-amide
or 5-Chloro-1H-indole-2-carboxylic acid ((1S)-**benzyl**
-(2R)-hydroxy-3-morpholin-4-yl-3-oxo-propyl)-amide.

13. The compound as recited in claim 11 wherein R.sub.1 is 5-chloro; R.sub.10 and R.sub.11 are H; R.sub.4 is **benzyl**; and R.sub.12 is 4-methylpiperazin-1-yl.

14. The compound as recited in claim 11 wherein R.sub.1 is 5-chloro; R.sub.10 and R.sub.11 are H; R.sub.4 is **benzyl**; and R.sub.12 is 3-hydroxyazetidin-1-yl.

15. The compound as recited in claim 11 wherein R.sub.1 is 5-chloro; R.sub.10 and R.sub.11 are H; R.sub.4 is **benzyl**; and R.sub.12 is isoxazolidin-2-yl.

16. The compound as recited in claim 11 wherein R.sub.1 is 5-chloro; R.sub.10 and R.sub.11 are H; R.sub.4 is **benzyl**; and R.sub.12 is (1,2)-oxazinan-2-yl.

17. The compound as recited in claim 11 wherein R.sub.1 is 5-chloro; R.sub.10 and R.sub.11 are H; R.sub.4 is **benzyl**; and R.sub.12 is 3(S)-hydroxypyrrolidin-1-yl.

18. The compound as recited in claim 11 wherein R.sub.1 is 5-chloro; R.sub.10 and R.sub.11 are H; R.sub.4 is **benzyl**; and R.sub.12 is (3S,4S)-dihydroxypyrrolidin-1-yl.

19. The compound as recited in claim 11 wherein R.sub.1 is 5-chloro; R.sub.10 and R.sub.11 are H; R.sub.4 is **benzyl**; and R.sub.12 is (3R4S)-dihydroxypyrrolidin-1-yl.

20. The compound as recited in claim 11 wherein R.sub.1 is 5-chloro; R.sub.10and R.sub.11 are H; R.sub.4 is **benzyl**; and R.sub.12 is morpholino.

21. A compound as recited in claim 1 wherein R.sub.1 is H, halo, **methyl** or cyano; R.sub.10 and R.sub.11 are each independently H or halo; A is --C(H).dbd.; R.sub.2 and R.sub.3 are H; R.sub.4. . . . . 23. The compound as recited in claim 22 wherein R.sub.1 is 5-chloro; R.sub.10 and R.sub.11 are H; and R.sub.4 is **benzyl**.

24. A compound as recited in claim 1 wherein R.sub.1 is H, halo, **methyl** or cyano; R.sub.10 and R.sub.11 are each independently H or halo; A is --C(H).dbd.; R.sub.2 and R.sub.3 are H; R.sub.4. . .
25. A compound as recited in claim 1 wherein R.sub.1 is H, halo, **methyl** or cyano; R.sub.10 and R.sub.11 are each independently H or halo; A is --C(H).dbd.; R.sub.2 and R.sub.3 are H; R.sub.4. . .
28. The method as recited in claim 26 for treating **diabetes** in a mammal by administering to a mammal suffering from **diabetes** a **diabetes** treating amount of a compound of claim 1.

L3 ANSWER 11 OF 15 USPATFULL on STN
AN 2002:27439 USPATFULL
TI Treatment of **diabetes** with thiazolidinedione; insulin

secretagogue and diguanide
IN Buckingham, Robin Edwin, Wel Wyn Garden City, UNITED KINGDOM
Smith, Stephen Alistair, Bramfield, UNITED KINGDOM
PA SmithKline Beecham p.l.c. (non-U.S. corporation)
PI US 2002016287 A1 20020207
AI US 2001-939470 A1 20010824 (9)
RLI Continuation of Ser. No. US 1999-446039, filed on 15 Dec 1999, PENDING A 371 of International Ser. No. WO 1999-GB9802110, filed on 28 Jan 1999, UNKNOWN
PRAI GB 1997-15295 19970718
DT Utility
FS APPLICATION
LREP GLAXOSMITHKLINE, Corporate Intellectual Property - UW2220, P.O. Box 1539, King of Prussia, PA, 19406-0939
CLMN Number of Claims: 22
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 479
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method for the treatment of **diabetes** mellitus and conditions associated with **diabetes** mellitus in a mammal, which method comprises administering an effective non-toxic and pharmaceutically acceptable amount of an insulin sensitiser, an insulin secretagogue and a biguanide antihyperglycaemic agent, to a mammal in need thereof; and composition for use in such method.
TI Treatment of **diabetes** with thiazolidinedione, insulin secretagogue and diguanide
AB A method for the treatment of **diabetes** mellitus and conditions associated with **diabetes** mellitus in a mammal, which method comprises administering an effective non-toxic and pharmaceutically acceptable amount of an insulin sensitiser, an. . .
SUMM [0001] This invention relates to a method of treatment, in particular to a method for the treatment of **diabetes** mellitus, especially non-insulin dependent **diabetes** (NIDDM) (or Type 2 **diabetes**) and conditions associated with **diabetes** mellitus.
SUMM . . . known examples of insulin secretagogues. The sulphonylureas act as antihyperglycaemic agents and are used in the treatment of Type 2 **diabetes**). Examples of sulphonylureas include glibenclamide, glipizide, gliclazide, **glimepiride**, tolazamide and tolbutamide.
SUMM [0004] Biguanide antihyperglycaemic agents are commonly used in the treatment of Type 2 **diabetes**). 1,1-Dimethylbiguanidine (or Metformin) is an example of a biguanide antihyperglycaemic agent.
SUMM . . . relates to certain thiazolidinedione derivatives disclosed as having antihyperglycaemic and antihyperlipidaemic activity. One particular thiazolidinedione disclosed in EP 0306228 is 5-[4-[2-(N-**methyl**-N-(2-**pyridyl**)amino)ethoxy]**benzyl**] **thiazolidine**-2,4-dione (hereinafter `Compound (I)`). WO94/05659 discloses certain salts of Compound (I) including the maleate salt.
SUMM . . . antihyperglycaemic agent provides a particularly beneficial effect on glycaemic control, such combination is therefore particularly useful for the treatment of **diabetes** mellitus, especially Type 2 **diabetes** and conditions associated with **diabetes** mellitus. The treatment is also indicated to proceed with minimum side effects.
SUMM [0012] Accordingly, the invention provides a method for the treatment of **diabetes** mellitus, especially Type 2 **diabetes**, and conditions associated with **diabetes** mellitus, in a mammal such as a human, which method comprises administering an effective non-toxic and pharmaceutically acceptable amount of. . .
SUMM . . . Compound (I), an insulin secretagogue and a biguanide

antihyperglycaemic agent, in the manufacture of a composition for the treatment of **diabetes** mellitus, especially Type 2 **diabetes** and conditions associated with **diabetes** mellitus.

SUMM [0018] Other suitable thiazolidinedione insulin sensitisers include (+)-5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]**methyl**]-2,4-thiazolidinedione (or troglitazone), 5-[4-[(1-methylcyclohexyl)methoxy]**benzyl**] **thiazolidine**-2,4-dione (or ciglitazone), 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]**benzyl**] **thiazolidine**-2,4-dione (or pioglitazone) or 5-[(2-**benzyl**-2,3-dihydrobenzopyran)-5-ylmethyl)**thiazolidine**-2,4-dione (or englitazone).

SUMM [0020] Suitable sulphonylureas include glibenclamide, glipizide, gliclazide, **glimepiride**, tolazamide and tolbutamide.

SUMM [0024] In one particular aspect, the method comprises the administration of 2 to **12 mg** of Compound (I), especially when administered per day.

SUMM [0025] Particularly, the method comprises the administration of 2 to 4, 4 to 8 or 8 to **12 mg** of Compound (I) per day.

SUMM [0028] Particularly, the method comprises the administration of 8 to **12 mg** of Compound (I), especially when administered per day.

DETD [0039] When used herein the term `conditions associated with **diabetes**` includes conditions associated with **diabetes** mellitus itself and complications associated with **diabetes** mellitus. Also included in `conditions associated with **diabetes** ` are those conditions associated with the pre-diabetic state.

DETD [0041] `Conditions associated with **diabetes** mellitus itself` include hyperglycaemia, insulin resistance, including acquired insulin resistance. Further conditions associated with **diabetes** mellitus itself include hypertension and cardiovascular disease, especially atherosclerosis and conditions associated with insulin resistance. Conditions associated with insulin resistance include polycystic ovarian syndrome and steroid induced insulin resistance and gestational **diabetes**.

DETD [0042] `Complications associated with **diabetes** mellitus` includes renal disease, especially renal disease associated with Type 2 **diabetes**, neuropathy and retinopathy.

DETD [0043] Renal diseases associated with Type 2 **diabetes** include nephropathy, glomerulonephritis, glomerular sclerosis, hypertensive nephrosclerosis and end stage renal disease. Additional renal diseases associated with Type 2 **diabetes** include nephrotic syndrome.

DETD [0045] **Diabetes** mellitus is preferably Type 2 **diabetes** .

DETD . . . the present invention also provides a pharmaceutical composition comprising an insulin sensitiser, such as Compound (I) and especially 2 to **12 mg** thereof, an insulin secretagogue and a biguanide antihyperglycaemic agent and a pharmaceutically acceptable carrier therefor.

DETD [0053] Such compositions may be prepared by admixing an insulin sensitiser, such as Compound (I) and especially 2 to **12 mg** thereof, an insulin secretagogue and a biguanide antihyperglycaemic agent and a pharmaceutically acceptable carrier therefor.

DETD . . . dosages, including unit dosages, of Compound (I) comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or **12 mg** of Compound (I).

DETD . . . other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, **methyl** cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin,

sorbitan monooleate, or acacia; non-aqueous. . . almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example **methyl** or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

DETD . . . The present invention also provides a pharmaceutical composition comprising an insulin sensitiser, such as Compound (I) and especially 2 to **12 mg** thereof, an insulin secretagogue and a biguanide antihyperglycaemic agent and a pharmaceutically acceptable carrier therefor, for use as an active. .

.

DETD [0074] The invention also provides the use of an insulin sensitiser, such as Compound (I) and especially 2 to **12 mg** thereof, an insulin secretagogue and a biguanide antihyperglycaemic agent for the manufacture of a medicament for the treatment of **diabetes** mellitus and conditions associated with **diabetes**.

DETD . . . particular, the present invention provides a pharmaceutical composition comprising an insulin sensitiser, such as Compound (I) and especially 2 to **12 mg** thereof, an insulin secretagogue and a biguanide antihyperglycaemic agent and a pharmaceutically acceptable carrier therefor, for use in the treatment of **diabetes** mellitus and conditions associated with **diabetes** mellitus.

DETD [0078] A range of 8 to **12 mg** includes a range of 8.1 to 12, 8.2 to 12, 8.3 to 12, 8.4 to 12, 8.5 to 12, 8.6 to 12, 8.7 to 12, 8.8 to 12, 8.9 to 12, 9to 12, 10 to 12 or 11 to **12 mg**

.

CLM What is claimed is:

1. A method for the treatment of **diabetes** mellitus and conditions associated with **diabetes** mellitus in a mammal, which method comprises administering an effective non-toxic and pharmaceutically acceptable amount of an insulin sensitiser, an. . .

2. A method according to claim 1, wherein the insulin secretagogue is glibenclamide, glipizide, gliclazide, **glimepiride**, tolazamide, tolbutamide, acetohexamide, carbutamide, chlorpropamide, glibornuride, gliquidone, glisentide, glisolamide, glisoxepide, glyclopyamide, glycylamide or repaglinide.

4. A method according to any one of claims 1 to 3, wherein the insulin sensitiser is 5-[4-[2-(N-**methyl**-N-(2-**pyridyl**)amino)ethoxy]**benzyl**]**thiazolidine**-2,4-dione (Compound I).

5. A method according to any one of claims 1 to 4, which comprises the administration of 2 to **12 mg** of Compound (I).

. . . one of claims 1 to 5, which comprises the administration of 2 to 4, 4 to 8 or 8 to **12 mg** of Compound (I).

9. A method according to any one of claims 1 to 6, which comprises the administration of 8 to **12 mg** of Compound (I).

13. A method according to claim 1, wherein the insulin sensitiser is (+)-5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]**methyl**]-2,4-thiazolidinedione (or troglitazone), 5-[4-[(1-methylcyclohexyl)methoxy]**benzyl**] **thiazolidine**-2,4-dione (or ciglitazone), 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]**benzyl**] **thiazolidine**-2,4-dione (or pioglitazone) or 5-[(2-**benzyl**-2,3-dihydrobenzopyran)-5-ylmethyl)**thiazolidine**-2,4-dione (or englitazone); or a pharmaceutically acceptable form thereof.

16. A composition according to claim 14 or claim 15, wherein the insulin secretagogue is glibenclamide, glipizide, gliclazide, **glimepiride**, tolazamide or tolbutamide, acetohexamide, carbutamide, chlorpropamide, glibornuride, gliquidone, glisentide, glisolamide, glisoxepide, glyclopyamide, glycylamide or repaglinide.

19. A composition according to any one of claims 14 to 17, which comprises 2 to **12 mg** of Compound (I).

. . . sensitiser, an insulin secretagogue, a biguanide antihyperglycaemic agent and a pharmaceutically acceptable carrier therefor, for use in the treatment of **diabetes** mellitus and conditions associated with **diabetes** mellitus.

22. A composition according to any one of claims 14, 20 or 21, wherein the insulin sensitiser is (+)-5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]**methyl**]-2,4-thiazolidinedione (or troglitazone), 5-[4-[(1-methylcyclohexyl)methoxy]**benzyl**] **thiazolidine**-2,4-dione (or ciglitazone), 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]**benzyl**] **thiazolidine**-2,4-dione (or pioglitazone) or 5-[(2-**benzyl**-2,3-dihydrobenzopyran)-5-ylmethyl) **thiazolidine**-2,4-dione (or englitazone); or a pharmaceutically acceptable form thereof.

L3 ANSWER 12 OF 15 USPATFULL on STN
AN 2001:224163 USPATFULL
TI Treatment of **diabetes** with thiazolidinedione and sulphonylurea
IN Smith, Stephen Alistair, Bramfield, Great Britain
PI US 2001049380 A1 20011206
AI US 2001-848511 A1 20010502 (9)
RLI Continuation of Ser. No. US 1999-445859, filed on 15 Dec 1999, ABANDONED A 371 of International Ser. No. WO 1998-EP3688, filed on 15 Jun 1998, UNKNOWN
PRAI GB 1997-12854 19970618
GB 1998-6710 19980327
DT Utility
FS APPLICATION
LREP SMITHKLINE BEECHAM CORPORATION, CORPORATE INTELLECTUAL PROPERTY-US, UW2220, P. O. BOX 1539, KING OF PRUSSIA, PA, 19406-0939
CLMN Number of Claims: 21
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 464
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method for the treatment of **diabetes** mellitus and conditions associated with **diabetes** mellitus in a mammal, which method comprises administering an effective non-toxic and pharmaceutically acceptable amount of an insulin sensitizer and an insulin secretagogue, to a mammal in need thereof.
TI Treatment of **diabetes** with thiazolidinedione and sulphonylurea
AB A method for the treatment of **diabetes** mellitus and conditions associated with **diabetes** mellitus in a mammal, which method comprises administering an effective non-toxic and pharmaceutically acceptable amount of an insulin sensitizer and. . .
SUMM [0001] This invention relates to a method of treatment, in particular to a method for the treatment of **diabetes** mellitus, especially non-insulin dependent **diabetes** (NIDDM) or Type II **diabetes** and conditions associated with **diabetes** mellitus.
SUMM . . . of insulin secretagogues. The sulphonylureas act as

hypoglycaemic agents and are used in the treatment of NIDDM (or Type II **diabetes**). Examples of sulphonylureas include glibenclamide, glipizide, gliclazide, **glimepiride**, tolazarnide and tolbutamide.

SUMM . . . relates to certain thiazolidinedione derivatives disclosed as having antihyperglycaemic and antihyperlipidaemic activity. One particular thiazolidinedione disclosed in EP 0306228 is 5-[4-[2-(N-**methyl**-N-(2-**pyridyl**)amino)ethoxy]**benzyl**] **thiazolidine**-2,4-dione (hereinafter `Compound (I)`). WO94/05659 discloses certain salts of Compound (I) including the maleate salt at example 1 thereof.

SUMM . . . insulin secretagogue provides a particularly beneficial effect on glycaemic control such combination is therefore particularly useful for the treatment of **diabetes** mellitus, especially Type II **diabetes** and conditions associated with **diabetes** mellitus. The treatment is also indicated to proceed with minimum side effects.

SUMM [0011] Accordingly, the invention provides a method for the treatment of **diabetes** mellitus, especially Type II **diabetes** and conditions associated with **diabetes** mellitus in a mammal such as a human, which method comprises administering an effective non-toxic and pharmaceutically acceptable amount of. . .

SUMM . . . insulin sensitiser, such as Compound (I), together with an insulin secretagogue for use in a method for the treatment of **diabetes** mellitus, especially Type II **diabetes** and conditions associated with **diabetes** mellitus.

SUMM . . . such as Compound (I), and an insulin secretagogue for use in the manufacture of a composition for the treatment of **diabetes** mellitus, especially Type II **diabetes** and conditions associated with **diabetes** mellitus.

SUMM [0017] Suitable sulphonylureas include glibenclamide, glipizide, gliclazide, **glimepiride**, tolazamide and tolbutamide.

SUMM [0021] Other suitable thiazolidinedione insulin sensitisers include (+)-5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]**methyl**]-2,4-thiazolidinedione (or troglitazone), 5-[4-[(1-methylcyclohexyl)methoxy]**benzyl**] **thiazolidine**-2,4-dione (or ciglitazone), 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]**benzyl**]**thiazolidine**-2,4-dione (or pioglitazone) or 5-[(2-**benzyl**-2,3-dihydrobenzopyran)-5-ylmethyl)**thiazolidine**-2,4-dione (or englitazone).

SUMM [0022] In one particular aspect, the method comprises the administration of 2 to **12 mg** of Compound (I), especially when administered per day.

SUMM [0023] Particularly, the method comprises the administration of 2 to 4, 4 to 8 or 8 to **12 mg** of Compound (I) per day.

SUMM [0026] Particularly, the method comprises the administration of 8 to **12 mg** of Compound (I), especially when administered per day.

SUMM [0037] When used herein the term `conditions associated with **diabetes**` includes those conditions associated with **diabetes** mellitus itself and complications associated with **diabetes** mellitus.

SUMM [0038] `Conditions associated with **diabetes** mellitus itself` include hyperglycaemia, insulin resistance, including acquired insulin resistance and obesity. Further conditions associated with **diabetes** mellitus itself include hypertension and cardiovascular disease, especially atherosclerosis and conditions associated with insulin resistance. Conditions associated with insulin resistance include polycystic ovarian syndrome and steroid induced insulin resistance and gestational **diabetes**.

SUMM [0039] `Complications associated with **diabetes** mellitus` includes renal disease, especially renal disease associated with Type II

diabetes, neuropathy and retinopathy.

SUMM [0040] Renal diseases associated with Type II **diabetes** include nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal disease.

SUMM [0043] **Diabetes** mellitus is preferably Type II **diabetes**.

SUMM . . . aspect the present invention also provides a pharmaceutical composition comprising an insulin sensitiser, such as Compound (I) especially 2 to **12 mg** thereof, an insulin secretagogue and a pharmaceutically acceptable carrier therefor.

SUMM [0050] Such compositions may be prepared by admixing an insulin sensitiser, such as Compound (I) especially 2 to **12 mg** thereof, the insulin secretagogue and a pharmaceutically acceptable carrier therefor.

SUMM . . . dosages of the Compound of formula (I) comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or **12 mg** of Compound (I).

DETD . . . other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, **methyl** cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous. . . almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example **methyl** or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

DETD [0069] The present invention also provides a pharmaceutical composition comprising an insulin sensitiser, such as Compound (I) especially 2 to **12 mg** thereof, an insulin secretagogue and a pharmaceutically acceptable carrier therefor, for use as an active therapeutic substance.

DETD . . . In particular, the present invention provides a pharmaceutical composition comprising an insulin sensitiser, such as Compound (I) especially 2 to **12 mg** thereof, an insulin secretagogue and a pharmaceutically acceptable carrier therefor, for use in the treatment of **diabetes** mellitus, especially Type II **diabetes** and conditions associated with **diabetes** mellitus.

DETD [0073] A range of 8 to **12 mg** includes a range of 8.1 to 12, 8.2 to 12, 8.3 to 12, 8.4 to 12, 8.5 to 12, 8.6. . . to 12, 8.7 to 12, 8.8 to 12, 8.9 to 12, 9 to 12, 10 to 12 or 11 to **12 mg**.

CLM What is claimed is:

1. A method for the treatment of **diabetes** mellitus and conditions associated with **diabetes** mellitus in a mammal, which method comprises administering an effective non-toxic and pharmaceutically acceptable amount of an insulin sensitiser and. . .

3. A method according to claim 1, wherein the insulin secretagogue is glibenclamide, glipizide, gliclazide, **glimepiride**, tolazamide or tolbutamide.

4. A method according to any one of claims 1 to 3, wherein the insulin sensitiser is 5-[4-[2-(N-**methyl**-N-(2-**pyridyl**)amino)ethoxy]**benzyl**]**thiazolidine**-2,4-dione (Compound I).

5. A method according to any one of claims 1 to 4, which comprises the administration of 2 to **12 mg** of Compound (1).

. . . one of claims 1 to 5, which comprises the administration of 2 to 4, 4 to 8 or 8 to **12 mg** of Compound (I).

9. A method according to any one of claims 1 to 6, which comprises the administration of 8 to **12 mg** of Compound (1).

13. A method according to claim 1, wherein the insulin sensitiser is (+)-5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]**methyl**]-2,4-thiazolidinedione (or troglitazone), 5-[4-[(1-methylcyclohexyl)methoxy]**benzyl**] **thiazolidine**-2,4-dione (or ciglitazone), 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]**benzyl**]**thiazolidine**-2,4-dione (or pioglitazone) or 5-[(2-**benzyl**-2,3-dihydrobenzopyran)-5-ylmethyl)**thiazolidine**-2,4-dione (or englitazone); or a pharmaceutically acceptable form thereof.

16. A composition according to claim 14 or claim 15, wherein the insulin secretagogue is glibenclamide, glipizide, gliclazide, **glimepiride**, tolazamide or tolbutamide.

18. A composition according to any one of claims 14 to 17, which comprises 2 to **12 mg** of Compound (I).

. . . composition comprising an insulin sensitiser, an insulin secretagogue and a pharmaceutically acceptable carrier therefor, for use in the treatment of **diabetes** mellitus and conditions associated with **diabetes** mellitus.

21. A composition according to any one of claims 14, 20 or 21, wherein the insulin sensitiser is (+)-5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]**methyl**]-2,4-thiazolidinedione (or troglitazone), 5-[4-[(1-methylcyclohexyl)methoxy]**benzyl**] **thiazolidine**-2,4-dione (or ciglitazone), 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]**benzyl**]**thiazolidine**-2,4-dione (or pioglitazone) or 5-[(2-**benzyl**-2,3-dihydrobenzopyran)-5-ylmethyl)**thiazolidine**-2,4-dione (or englitazone); or a pharmaceutically acceptable form thereof.

L3 ANSWER 13 OF 15 USPATFULL on STN
AN 2001:168152 USPATFULL
TI Substituted n-(indole-2-carbonyl-) amides and derivatives as glycogen phosphorylase inhibitors
IN Hulin, Bernard, Essex, CT, United States
Hoover, Dennis J., Stonington, CT, United States
Treadway, Judith L., Gales Ferry, CT, United States
Martin, William H., Essex, CT, United States
PA Pfizer Inc., New York, NY, United States (U.S. corporation)
PI US 6297269 B1 20011002
WO 9639385 19961212
AI US 1997-952668 19971202 (8)
WO 1995-IB443 19950606
19971202 PCT 371 date
19971202 PCT 102(e) date
DT Utility
FS GRANTED
EXNAM Primary Examiner: Ramsuer, Robert W.; Assistant Examiner: Keating, Domenik
LREP Richardson, Peter C., Benson, Gregg C., Olson, A. Dean
CLMN Number of Claims: 77
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 4318
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compounds of the formula I: ##STR1##

and their compositions are useful as glycogen phosphorylase inhibitors.

SUMM This invention relates to glycogen phosphorylase inhibitors, pharmaceutical compositions containing such inhibitors and the use of such inhibitors to treat **diabetes**, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemias, hyperlipidemia, atherosclerosis and myocardial ischemia in mammals.

SUMM In spite of the early discovery of insulin and its subsequent widespread use in the treatment of **diabetes**, and the later discovery of and use of sulfonylureas (e.g. Chlorpropamide.TM. (Pfizer), Tolbutamide.TM. (Upjohn), Acetohexamide.TM. (E. I. Lilly), Tolazamide.TM. (Upjohn)) and biguanides (e.g. Phenformin.TM. (Ciba Geigy), Metformin.TM. (G. D. Searle)) as oral hypoglycemic agents, the treatment of **diabetes** remains less than satisfactory. The use of insulin, necessary in about 10% of diabetic patients in which synthetic hypoglycemic agents are not effective (Type I **diabetes** , insulin dependent **diabetes** mellitus), requires multiple daily doses, usually by self injection. Determination of the proper dosage of insulin requires frequent estimations of. . . causes hypoglycemia, with effects ranging from mild abnormalities in blood glucose to coma, or even death. Treatment of non-insulin dependent **diabetes** mellitus (Type II **diabetes**, NIDDM) usually consists of a combination of diet, exercise, oral agents, e.g. sulfonylureas, and in more severe cases, insulin. However,. . .

SUMM . . . whom the causative agent or disorder is unknown. While such "essential" hypertension is often associated with disorders such as obesity, **diabetes** and hypertriglyceridemia, the relationship between these disorders has not been elucidated. Additionally, many patients display the symptoms of high blood. . .

SUMM This invention is directed to glycogen phosphorylase inhibitor compounds of Formula I useful for the treatment of **diabetes**, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis and myocardial ischemia.

SUMM R.sub.4 is H, **methyl**, ethyl, n-propyl, hydroxy(C.sub.1 -C.sub.3)alkyl, (C.sub.1 -C.sub.3)alkoxy(C.sub.1 -C.sub.3)alkyl, phenyl(C.sub.1 -C.sub.4)alkyl, phenylhydroxy(C.sub.1 -C.sub.4)alkyl, phenyl(C.sub.1 -C.sub.4)alkoxy(C.sub.1 -C.sub.4)alkyl, thien-2- or -3-yl(C.sub.1 -C.sub.4)alkyl or fur-2-. . .

SUMM R.sub.9 is H, (C.sub.1 -C.sub.8)alkyl, hydroxy, (C.sub.1 -C.sub.8)alkoxy, methylene-perfluorinated(C.sub.1 -C.sub.8)alkyl, phenyl, **pyridyl**, thienyl, furyl, pyrrolyl, pyrrolidinyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, pyranyl, piperidinyl, morpholinyl, pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl or. . .

SUMM R.sub.9 is mono- or di-substituted (C.sub.1 -C.sub.5)alkyl, wherein said substituents are independently phenyl, **pyridyl**, furyl, pyrrolyl, pyrrolidinyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, pyranyl, pyridinyl, piperidinyl, morpholinyl, pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl or. . .

SUMM wherein the nonaromatic nitrogen-containing R.sub.9 rings are optionally mono-substituted on nitrogen with (C.sub.1 -C.sub.6)alkyl, **benzyl**, benzoyl or (C.sub.1 -C.sub.6)alkoxycarbonyl and wherein the R.sub.9 rings are optionally mono-substituted on carbon with halo, (C.sub.1 -C.sub.4)alkyl, (C.sub.1 -C.sub.4)alkoxy,. . .

SUMM with the proviso that if R.sub.4 is H, **methyl**, ethyl or n-propyl R.sub.5 is OH;

SUMM with the proviso that if R.sub.5 and R.sub.7 are H, then R.sub.4 is not H, **methyl**, ethyl, n-propyl, hydroxy(C.sub.1 -C.sub.3)alkyl or (C.sub.1 -C.sub.3)alkoxy(C.sub.1 -C.sub.3)alkyl and R.sub.6 is C(O)NR.sub.8 R.sub.9, C(O)R.sub.12 or (C.sub.1 -C.sub.4)alkoxycarbonyl.

SUMM R.sub.1 is 5-H, 5-halo, 5-**methyl** or 5-cyano;
SUMM R.sub.9 is H, (C.sub.1 -C.sub.8)alkyl, hydroxy, hydroxy(C.sub.1 -C.sub.6)alkyl, (C.sub.1 -C.sub.8)alkoxy, **pyridyl**, morpholinyl, piperazinyl, pyrrolidinyl, piperidinyl, imidazolyl or thiazolyl or (C.sub.1 -C.sub.4)alkyl mono-substituted with **pyridyl**, morpholinyl, piperazinyl, pyrrolidinyl, piperidinyl, imidazolyl or thiazolyl.
SUMM 5-Chloro-1H-indole-2-carboxylic acid [(1S)-((R)-hydroxy-dimethylcarbamoyl-**methyl**)-2-phenyl-ethyl]-amide,
SUMM 5,6-Dichloro-1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(methoxy-**methyl**-carbamoyl)-**methyl**]-2-phenyl-ethyl}-amide,
SUMM 5-Chloro-1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(methoxy-**methyl**-carbamoyl)-**methyl**]-2-phenyl-ethyl}-amide,
SUMM 5-Chloro-1H-indole-2-carboxylic acid ((1S)-{(R)-hydroxy-[(2-hydroxy-ethyl)-**methyl**-carbamoyl]-**methyl**}-2-phenyl-ethyl)-amide,
SUMM 5-Chloro-1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(**methyl**-pyridin-2-yl-carbamoyl)-**methyl**]-2-phenyl-ethyl}-amide or
SUMM 5-Chloro-1H-indole-2-carboxylic acid ((1S)-{(R)-hydroxy-[**methyl**-(2-pyridin-2-yl-ethyl)-carbamoyl]-**methyl**}-2-phenyl-ethyl)-amide.
SUMM R.sub.4 is **benzyl**;
SUMM R.sub.8 is **methyl**; and
SUMM R.sub.9 is **methyl**;
SUMM R.sub.4 is **benzyl**;
SUMM R.sub.8 is **methyl**; and
SUMM R.sub.4 is **benzyl**;
SUMM R.sub.8 is **methyl**; and
SUMM R.sub.4 is **benzyl**;
SUMM R.sub.8 is **methyl**; and
SUMM R.sub.4 is **benzyl**;
SUMM R.sub.8 is **methyl**; and
SUMM R.sub.4 is **benzyl**;
SUMM R.sub.8 is **methyl**; and
SUMM 5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-(2R)-hydroxy-3-(4-methylpiperazin-1-yl)-3-oxo-propyl]-amide hydrochloride,
SUMM 5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-(2R)-hydroxy-3-(3-hydroxyazetidin-1-yl)-3-oxo-propyl]-amide,
SUMM 5-Chloro-1H-indole-2-carboxylic acid ((1S)-**benzyl**-(2R)-hydroxy-3-isoxazolidin-2-yl-3-oxo-propyl)-amide,
SUMM 5-Chloro-1H-indole-2-carboxylic acid ((1S)-**benzyl**-(2R)-hydroxy-3-[1,2]oxazinan-2-yl-3-oxo-propyl)-amide,
SUMM 5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-(2R)-hydroxy-3-((3S)-hydroxy-pyrrolidin-1-yl)-3-oxo-propyl]-amide,
SUMM 5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-3-((3S,4S)-dihydroxypyrrolidin-1-yl)-(2R)-hydroxy-3-oxo-propyl]-amide,
SUMM 5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-3-((3R,4S)-dihydroxypyrrolidin-1-yl)-(2R)-hydroxy-3-oxo-propyl]-amide or
SUMM 5-Chloro-1H-indole-2-carboxylic acid ((1S)-**benzyl**-(2R)-hydroxy-3-morpholin-4-yl-3-oxo-propyl)-amide.
SUMM R.sub.4 is **benzyl**; and
SUMM R.sub.4 is **benzyl**; and
SUMM R.sub.4 is **benzyl**; and
SUMM R.sub.4 is **benzyl**; and
SUMM R.sub.4 is **benzyl**; and
SUMM R.sub.4 is **benzyl**; and
SUMM R.sub.4 is **benzyl**; and
SUMM R.sub.4 is **benzyl**; and
SUMM R.sub.1 is H, halo, **methyl** or cyano;
SUMM R.sub.4 is **benzyl**.

SUMM R.sub.1 is H, halo, **methyl** or cyano;

SUMM R.sub.1 is H, halo, **methyl** or cyano;

SUMM Yet another aspect of this invention is directed to a method for treating **diabetes** in a mammal by administering to a mammal suffering from **diabetes** a **diabetes** treating amount of a Formula I compound.

SUMM . . . to a mammal suffering from hypercholesterolemia a hypercholesterolemia treating amount of a Formula I compound. Included in the treatment of **diabetes** is the prevention or attenuation of long term complications such as neuropathy, nephropathy, retinopathy or cataracts.

SUMM Another aspect of this invention is directed to pharmaceutical compositions for the treatment of **diabetes** which comprise a therapeutically effective amount of a glycogen phosphorylase inhibitor;

SUMM . . . analogs (e.g. LysPro insulin); GLP-1 (7-37) (insulinotropin) and GLP-1 (7-36)-NH.sub.2 ; Sulfonylureas and Analogs: chlorpropamide, glibenclamide, tolbutamide, tolazamide, acetohexamide, glypizide.RTM., **glimepiride**, repaglinide, meglitinide; Biguanides: metformin, phenformin, buformin; .alpha.2-Antagonists and Imidazolines: midaglizole, isaglidole, deriglidole, idazoxan, efaroxan, fluparoxan; Other insulin secretagogues: linogliride, A-4166;. . .

SUMM Another aspect of this invention is a method of treating **diabetes** in a mammal with the above described combination compositions.

SUMM . . . glycogen molecule. These disorders are ameliorated by reduction of or characterized by an elevation of glycogen phosphorylase activity. Examples include **diabetes**, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis and myocardial ischemia.

SUMM . . . straight chain or branched saturated hydrocarbon. Exemplary of such alkyl groups (assuming the designated length encompasses the particular example) are **methyl**, ethyl, propyl, isopropyl, butyl, sec-butyl, tertiary butyl, pentyl, isopentyl, hexyl and isohexyl.

SUMM . . . such as (but not limited to) sodium, potassium, calcium, magnesium, ammonium or protonated benzathine (N,N'-dibenzylethylenediamine), choline, ethanolamine, diethanolamine, ethylenediamine, meglamine (N-**methyl**-glucamine), benethamine (N-benzylphenethylamine), piperazine or tromethamine (2-amino-2-hydroxymethyl-1,3-propanediol).

SUMM . . . carboxy) wherein the free hydrogen is replaced by (C.sub.1 -C.sub.4)alkyl, (C.sub.2 -C.sub.12)alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-**methyl** -1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-**methyl**-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to. . .

SUMM . . . I wherein the free hydrogen of the hydroxy substituent (e.g., R.sub.5 is hydroxy) is replaced by (C.sub.1 -C.sub.6)alkanoyloxymethyl, 1-((C.sub.1 -C.sub.6)alkanoyloxy)ethyl, 1-**methyl**-1-((C.sub.1 -C.sub.6)alkanoyloxy)ethyl, (C.sub.1 -C.sub.6)alkoxycarbonyloxymethyl, N-(C.sub.1 -C.sub.6)alkoxycarbonylaminomethyl, succinoyl, (C.sub.1 -C.sub.6)alkanoyl, .alpha.-amino(C.sub.1 -C.sub.4)alkanoyl, arylactyl and .alpha.-aminoacyl, or .alpha.-aminoacyl-.alpha.-aminoacyl wherein said .alpha.-aminoacyl moieties are. . .

SUMM . . . free hydrogen which is replaced by R-carbonyl, RO-carbonyl, NRR'-carbonyl where R and R' are each independently ((C.sub.1 -C.sub.10)alkyl, (C.sub.3 -C.sub.7)cycloalkyl, **benzyl**, or R-carbonyl is a natural .alpha.-aminoacyl or natural .alpha.-aminoacyl-natural .alpha.-aminoacyl, --C(OH)C(O)OY wherein (Y is H, (C.sub.1 -C.sub.6)alkyl or **benzyl**), --C(OY.sub.0)Y.sub.1

wherein Y.sub.0 is (C.sub.1 -C.sub.4) alkyl and Y.sub.1 is ((C.sub.1 -C.sub.6)alkyl, carboxy(C.sub.1 -C.sub.6)alkyl, amino(C.sub.1 -C.sub.4)alkyl or mono-N- or di-N,N-(C.sub.1 -C.sub.6)alkylaminoalkyl, --C(Y.sub.2)Y.sub.3 wherein Y2 is H or **methyl** and Y.sub.3 is mono-N- or di-N,N-(C.sub.1 -C.sub.6)alkylamino, morpholino, piperidin-1-yl or pyrrolidin-1-yl.

SUMM . . . those protecting groups commonly used in peptide synthesis (such as N-t-butoxycarbonyl, N-carbobenzyloxy, and 9-fluorenylmethylenoxycarbonyl for amines and lower alkyl or **benzyl** esters for carboxylic acids) which are not chemically reactive under the coupling conditions described above (and immediately preceding the Examples. . .

SUMM Alternatively, the Formula VIIIA indole 2-carboxylic acid may be prepared by condensation of a Formula IX ortho **methyl** nitro compound with an oxalate ester to yield the Formula X indole ester followed by reduction of the nitro group. . .

SUMM . . . is C(O)R.sub.12 or C(O)NR.sub.8 R.sub.9. An example of the conversion of a Formula XXI cyanohydrin to the corresponding Formula XXII **methyl** ester with removal of the t-boc protecting group is provided in PCT publication WO/9325574, Example 1a. Other examples wherein a. . .

SUMM For example, the preparation of the Formula XXI compound wherein P.sub.T is Boc, R.sub.3 is H, R.sub.4 is **benzyl** and the stereochemistry of carbons a and b is (S) and (R) respectively, employing this route together with purification by. . .

SUMM . . . group (P.sub.T) (such as Boc). The protected compound is esterified with an alcohol and converted to an ester, preferably the **methyl** or ethyl ester of the Formula XXXI compound. This may be accomplished by treating the Formula XXX compound with **methyl** or ethyl iodide in the presence of a suitable base (e.g., K.sub.2 CO.sub.3) in a polar solvent such as dimethylformamide.. . .

SUMM . . . Benoiton, Can. J. Chem 1977, 55, 906-910, and Hansen, J. Org. Chem. 1985, 50 945-950. For example, when R.sub.3 is **methyl**, sodium hydride and **methyl** iodide in tetrahydrofuran are utilized. Deprotection of the Formula XLI compound yields the desired Formula XXX compound.

SUMM . . . acid may be N-alkylated by a three-step sequence involving reductive benzylation (such as with benzaldehyde, Pd/C-catalyzed hydrogenation) to give the mono-N-**benzyl** derivative and reductive amination with the appropriate acyl compound (for example with formaldehyde and sodium cyanoborohydride to introduce R.sub.3 as **methyl**) to give the N-**Benzyl**, N-R.sub.3 -substituted amino acid. The N-**benzyl** protecting group is conveniently removed (for example by hydrogenation with an appropriate catalyst) to yield the Formula XXX compound. Specific. . .

SUMM . . . conditions, to give R.sub.8 R.sub.9 N(P.sub.T). The protecting group (P.sub.T) is removed (e.g. by exhaustive catalytic hydrogenation when P.sub.T is **benzyl**) to give a compound of formula R.sub.8 R.sub.9 NH. Appropriate reductive amination conditions are available from the literature to one. . .

SUMM N-(1-hydroxyalkyl) amides, N-(1-hydroxy-1-(alkoxycarbonyl)**methyl**) amides or compounds where R.sub.2 has been replaced by C(OH)C(O)OY may be prepared by the reaction of the parent amide. . .

SUMM . . . beads are then washed once with the same buffer prior to blocking with 50 mM HEPES and 1 M glycine **methyl** ester at pH 8.0 for one hour at room temperature. Blocking buffer is removed and replaced with 50 mM HEPES. . .

SUMM . . . group assignment, animals are dosed orally each day for four days with the vehicle consisting of either: 1) 0.25% w/v **methyl** cellulose in water without pH adjustment; or 2) 0.1% Pluronic.RTM. P105 Block Copolymer Surfactant (BASF Corporation, Parsippany, N.J.) in 0.1%. . . with the test compound or the vehicle alone. All drugs are

administered in vehicle consisting of either: 1) 0.25% w/v **methyl** cellulose in water without pH adjustment; or 2) 10% DMSO/0.1% Pluronic.RTM. P105 (BASF Corporation, Parsippany, N.J.) in 0.1% saline without. . .

DETD 5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-(2R)-hydroxy-3-(4-**methyl**-piperazin-1-yl)-3-oxo-propyl]-amide hydrochloride

DETD (3S)-Amino-(2R)-hydroxy-1-(4-**methyl**-piperazin-1-yl)-4-phenyl-butan-1-one dihydrochloride (0.25 mmol) and 5-chloro-1H-indole-2-carboxylic acid (0.30 mmol) were coupled according to Procedure A and the product purified by chromatography. . .

DETD (3S)-Amino-(2R)-hydroxy-1-(4-**methyl**-piperazin-1-yl)-4-phenyl-butan-1-one dihydrochloride

DETD [(1S)-**Benzyl**-(2R)-hydroxy-3-(4-**methyl**-piperazin-1-yl)-3-oxo-propyl]-carbamic acid tert-butyl ester (0.190 g, 0.5 mmol) was dissolved in 4 M HCl-dioxane at 25.degree. C. for 0.5 hours. The. . .

DETD [(1S)-**Benzyl**-(2R)-hydroxy-3-(4-**methyl**-piperazin-1-yl)-3-oxo-propyl]-carbamic acid tert-butyl ester

DETD 5-Chloro-1H-indole-2-carboxylic acid [(1S)-((R)-hydroxy-methylcarbamoyl-**methyl**)-2-phenyl-ethyl]-amide

DETD (3S)-[(5-Fluoro-1H-indole-2-carbonyl)-amino]-(2R)-hydroxy-4-phenyl-butyric acid **methyl** ester

DETD (3S)-Amino-(2R)-hydroxy-4-phenyl-butyric acid **methyl** ester (0.8 mmol, WO 9325574 Example 1A) and 5-fluoro-1H-indole-2-carboxylic acid (0.8 mmol) were coupled according to Procedure A (except at. . .

DETD (3S)-[(5-Bromo-1H-indole-2-carbonyl)-amino]-(2R)-hydroxy-4-phenyl-butyric acid **methyl** ester

DETD (3S)-Amino-(2R)-hydroxy-4-phenyl-butyric acid **methyl** ester (WO 93/25574, Example 1A) (0.7 mmol) and 5-bromo-1H-indole-2-carboxylic acid (0.7 mmol) were coupled according to Procedure A (except at. . .

DETD 5-Fluoro-1H-indole-2-carboxylic acid [(1S)-((R)-dimethylcarbamoyl-hydroxy-**methyl**)-2-phenyl-ethyl]-amide

DETD 5-Bromo-1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(methoxy-**methyl**-carbamoyl)-**methyl**]-2-phenyl-ethyl}-amide

DETD (3S)-Amino-(2R)-hydroxy-N-methoxy-N-**methyl**-4-phenyl-butyramide hydrochloride (0.36 mmol) and 3-[(5-bromo-1H-indole-2-carbonyl)-amino]-2-hydroxy -4-phenyl-butyric acid (0.36 mmol) were coupled according to Procedure A and the crude product purified. . .

DETD 5-Chloro-3-**methyl**-1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(methoxy-**methyl**-carbamoyl)-**methyl**]-2-phenyl-ethyl}-amide

DETD (3S)-Amino-(2R)-hydroxy-N-methoxy-N-**methyl**-4-phenyl-butyramide hydrochloride (0.3 mmol) and 5-chloro-3-**methyl**-1H-indole-2-carboxylic acid (0.3 mmol) were coupled according to Procedure A and the crude product purified by trituration with ether: Yield, 59%,. . .

DETD 5-Chloro-3-**methyl**-1H-indole-2-carboxylic acid

DETD 2N NaOH (20 mL) was added to a suspension of 5-chloro-3-**methyl**-1H-indole-2-carboxylic acid ethyl ester (7.0 g, 29.4 mmol) in methanol (50 mL) and the resulting mixture stirred at 25.degree. C. for. . .

DETD 5-Chloro-3-**methyl**-1H-indole-2-carboxylic acid ethyl ester

DETD (3S)-Amino-(2R)-hydroxy-N-methoxy-N-**methyl**-4-phenyl-butyramide hydrochloride 31055-274-2 31055-85-1

DETD {(1S)-[(R)-Hydroxy-(methoxy-**methyl**-carbamoyl)-**methyl**]-2-phenyl-ethyl}-carbamic acid tert-butyl ester (791 mg, 2.3 mmol) was dissolved in 4M HCl-dioxanes for 45 minutes at 25.degree. C. for 45. .

DETD {(1S)-[(R)-Hydroxy-(methoxy-**methyl**-carbamoyl)-**methyl**]-2-phenyl-ethyl}-carbamic acid tert-butyl ester

DETD (3S)-[(5,6-Dichloro-1H-indole-2-carbonyl)-amino]-(2R)-hydroxy-4-phenyl-butyric acid **methyl** ester

DETD (3S)-Amino-(2R)-hydroxy-4-phenyl-butyric acid **methyl** ester (1.2 mmol) and 5,6-dichloro-1H-indole-2-carboxylic acid (1.2 mmol) were coupled according to Procedure A (reaction time 72 hours) and the. . .

DETD . . . mL). The resulting solution was treated at 3.degree. C. with a solution of diethyl oxalate (10.0 g, 62 mmol) and 2-**methyl**-3,4-dichloro-1-nitrobenzene (10.0 g, 62 mmol) over 5-10 min, and the resulting solution stirred 30 minutes at 3.degree. C. and 25.degree. C.. . .

DETD 5-Cyano-1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(methoxy-**methyl**-carbamoyl)-**methyl**]-2-phenyl-ethyl}-amide

DETD (3S)-Amino-(2R)-hydroxy-N-methoxy-N-**methyl**-4-phenyl-butyramide hydrochloride (0.3 mmol) and 5-cyano-1H-indole-2-carboxylic acid (0.3 mmol) were coupled according to Procedure A (reaction time 5 days). The crude. . .

DETD . . . 400 ml ethanol) was added at 0.degree. C. to a mixture of distilled diethyl oxalate (120 g, 821 mmol) and 3-**methyl**-4-nitrobenzonitrile (32 g, 197 mmol). The resulting red solution was heated at 40.degree. C. for 18 hours. The cooled mixture was. . .

DETD 5-**Methyl**-1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(methoxy-**methyl**-carbamoyl)-**methyl**]-2-phenyl-ethyl}-amide

DETD (3S)-Amino-(2R)-hydroxy-N-methoxy-N-**methyl**-4-phenyl-butyramide hydrochloride (0.5 mmol) and 5-**methyl**-1H-indole-2-carboxylic acid (0.5 mmol) were coupled according to Procedure A (reaction temperature 0-25.degree. C., extraction with acid first, then base) and. . .

DETD 5-Fluoro-1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(methoxy-**methyl**-carbamoyl)-**methyl**]-2-phenyl-ethyl}-amide

DETD (3S)-Amino-(2R)-hydroxy-N-methoxy-N-**methyl**-4-phenyl-butyramide hydrochloride (0.5 mmol) and 5-fluoro-1H-indole-2-carboxylic acid (0.5 mmol) were coupled according to Procedure A (washing first with acid then base). . .

DETD 1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(methoxy-**methyl**-carbamoyl)-**methyl**]-2-phenyl-ethyl}-amide

DETD (3S)-Amino-(2R)-hydroxy-N-methoxy-N-**methyl**-4-phenyl-butyramide hydrochloride (0.26 mmol) and 1H-indole-2-carboxylic acid (0.28 mmol) were coupled according to Procedure A (0-25.degree. C. reaction temperature) and the. . .

DETD 5-Chloro-1H-indole-2-carboxylic acid {(1S)[(methoxy-**methyl**-carbamoyl)-**methyl**]-2-phenyl-ethyl}-amide

DETD 2N NaOH (3.0 mL) was added to a suspension of (3S)-[(5-chloro-1H-indole-2-carbonyl)-amino]-4-phenyl-butyric acid **methyl** ester (1.28 g, 3.45 mmol) in methanol (10 mL) at 25.degree. C. After 18 hours the reaction mixture was diluted. . .

DETD (3S)-[(5-Chloro-1H-indole-2-carbonyl)-amino]-(2R)-hydroxy-4-phenylbutyric acid **methyl** ester

DETD 1-(3-dimethylaminopropyl)3-ethylcarbodiimide hydrochloride (DEC, 71 g, 370 mmol) was added to a mixture of (3S)-amino-(2R)-hydroxy-4-phenyl-butyric acid **methyl** ester (WO 93/25574, Example 1A, 77.5 g, 370 mmol), 5-chloro-1H-indole-2-carboxylic acid (72.45 g, 370 mmol) and 1-hydroxybenzotriazole hydrate in dichloromethane. . .

DETD (RS)-3-amino-2-hydroxypropionic acid **methyl** ester hydrochloride (6.6 mmol) and 5-chloro-1H-indole-2-carboxylic acid (6.6 mmol) were coupled according to Procedure A (except that acid, then base. . .

DETD (RS)-3-amino-2-hydroxypropionic acid **methyl** ester hydrochloride

DETD 5-Chloro-1H-indole-2-carboxylic acid [(1S)-((R)-methoxy-methylcarbamoyl-**methyl**)-2-phenyl-ethyl]-amide

DETD (1S,2R)-(1-**Benzyl**-2-dimethylcarbamoyl-2-methoxy-ethyl)-carbamic acid tert-butyl ester (283 mg, 0.84 mmol) was dissolved in 4N HCl-dioxane (1 mL) for 1.5 hours at 25.degree. C.,. . .

DETD (1S,2R)-(1-**Benzyl**-2-dimethylcarbamoyl-2-methoxy-ethyl)-carbamic acid tert-butyl ester

DETD Sodium hydride-oil dispersion (53 mg of 50%) was added to a solution of (1S,2R)-(1-**benzyl**-2-dimethylcarbamoyl-2-hydroxy-ethyl)-carbamic acid tert-butyl ester (322 mg, 1.0 mmol) in tetrahydrofuran (4 mL) at 0.degree. C. After effervescence ceased (several minutes), **methyl** iodide (155 mg) was added, and after 15 minutes another 11 mg NaH dispersion and 23 mg **methyl** iodide were added. After 15 more minutes aqueous ammonium chloride solution and ethyl acetate were added, and the organic layer. . .

DETD (1S,2R)-(1-**Benzyl**-2-dimethylcarbamoyl-2-hydroxy-ethyl)-carbamic acid tert-butyl ester

DETD 5-Chloro-1H-indole-2-carboxylic acid (3-azetidin-1-yl-(1S)-**benzyl**-(2R)-hydroxy-3-oxo-propyl)-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-(2R)-methoxy-2-(methoxy-**methyl**-carbamoyl)-ethyl]-amide

DETD (3S,2R)-3-Amino-(2R),N-dimethoxy-N-**methyl**-4-phenyl-butyramide (0.31 mmol) and 5-chloro-1H-indole-2-carboxylic acid (0.31 mmol) were coupled according to Procedure A and the product purified by chromatography on. . .

DETD (3S,2R)-3-Amino-(2R), N-dimethoxy-N-**methyl**-4-phenyl-butyramide

DETD (1S,2R)-(1-**Benzyl**-2-methoxy-**methyl**-carbamoyl-2-methoxy-ethyl)-carbamic acid tert-butyl ester (113 mg, 0.32 mmol) was dissolved in 4N HCl-dioxane (4 mL) at 25.degree. C. for 1 hour,. . .

DETD (1S,2R)-(1-**Benzyl**-2-methoxy-**methyl**-carbamoyl-2-methoxy-ethyl)-carbamic acid tert-butyl ester

DETD Sodium hydride dispersion (30 mg of 50% in oil) was added to a solution of (1S,2R)-(1-**Benzyl**-2-methoxy-**methyl**-carbamoyl-2-hydroxy-ethyl)-carbamic acid tert-butyl ester in tetrahydrofuran (2 mL) at 0.degree. C. After 5 minutes **methyl** iodide (175 mg) was added and the mixture was allowed to stand at 25.degree. C. for 18 hour. Ethyl acetate. . .

DETD [(2S)-[(5-Chloro-1H-indole-2-carbonyl)-amino]-(1R)-(methoxy-**methyl**-carbamoyl)-3-phenyl-propoxy]-acetic acid **benzyl** ester

DETD (1R,2S)-[2-Amino-1-(methoxy-**methyl**-carbamoyl)-3-phenyl-propoxy]-acetic acid **benzyl** ester hydrochloride (162 mg, 0.38 mmol) was coupled with 5-chloro-1H-indole-2-carboxylic acid (71 mg, 0.36 mmol) according to Procedure A (0-25.degree.. . .

DETD (1R,2S)-[2-Amino-1-(methoxy-**methyl**-carbamoyl)-3-phenyl-propoxy]-acetic acid **benzyl** ester hydrochloride

DETD (1R,2S)-[2-tert-Butoxycarbonylamino-1-(methoxy-**methyl**-carbamoyl)-3-phenyl-propoxy]-acetic acid **benzyl** ester (170 mg, 0.35 mmol) was dissolved in 4N HCl-dioxane (2 mL) for 1.5 hours at 25.degree. C., concentrated, the. . .

DETD (1R,2S)-[2-tert-Butoxycarbonylamino-1-(methoxy-**methyl**-carbamoyl)-3-phenyl-propoxy]-acetic acid **benzyl** ester

DETD Sodium hydride dispersion (120 mg of 50% in oil, 2.8 mmol) was added to a solution of (1S,2R)-(1-**benzyl**-2-methoxy-**methyl**-carbamoyl-2-hydroxy-ethyl)-carbamic acid tert-butyl ester (858 mg, 2.5 mmol) in tetrahydrofuran (8 mL) at 0.degree. C. After effervescence ceased **benzyl** bromoacetate (0.56 g, 2.5 mmol) was added and the mixture was brought to 25.degree. C. After 2 hours more NaH dispersion was added (**12 mg**), and the mixture was stirred 1 hour, diluted with ethyl acetate and saturated ammonium chloride, the organic layer separated, washed. . .

DETD [(2S)-[(5-Chloro-1H-indole-2-carbonyl)-amino]-(1R)-(methoxy-**methyl**-carbamoyl)-3-phenyl-propoxy]-acetic acid

DETD A mixture of [(2S)-[(5-chloro-1H-indole-2-carbonyl)-amino]-(1R)-(methoxy-**methyl**-carbamoyl)-3-phenyl-propoxy]-acetic acid **benzyl** ester (120 mg, 0.2 mmol) and 50% moist palladium hydroxide on carbon

catalyst in methanol (50 mL) was shaken at. . . a solid, HPLC (60/40) 4.81 (37%) and 6.24 minutes (63%). .sup.1 H NMR and MS analysis showed these to be **methyl** esters of the 5-des-Cl and title product respectively. This solid was dissolved in THF and treated with 1N NaOH (170. . .

DETD [(1S)-((S)-Carbamoyl-hydroxy-**methyl**)-2-phenyl-ethyl]-carbamic acid tert-butyl ester (0.50 g, 1.7 mmol) was dissolved in 4 M HCl-dioxane at 25.degree. C. for 1 hour. The. . .

DETD [(1S)-((S)-Carbamoyl-hydroxy-**methyl**)-2-phenyl-ethyl]-carbamic acid tert-butyl ester

DETD Tetrabutylammonium fluoride (23 mL of 1M in tetrahydrofuran) was added to a solution of {(1S)-[(S)-(tert-butyl-dimethyl-silanyloxy)-carbamoyl-**methyl**]-2-phenyl-ethyl}-carbamic acid tert-butyl ester in tetrahydrofuran (6 mL) at 0.degree. C. After 30 minutes the mixture was diluted with ethyl acetate. . .

DETD {(1S)-[(S)-(tert-Butyl-dimethyl-silanyloxy)-carbamoyl-**methyl**]-2-phenyl-ethyl}-carbamic acid tert-butyl ester

DETD 30% hydrogen peroxide (7.2 mL, 64 mmol) was added over a period of 15 minutes to a solution of [1(S)-**benzyl**-(2S)-(tert-butyl-dimethyl-silanyloxy)-2-cyano-ethyl]-carbamic acid tert-butyl ester (Example 24D, 5.0 g, 12.8 mmol) and 1N NaOH (22 mL) in ethanol (110 mL) at 0.degree.. . .

DETD 5-Chloro-1H-indole-2-carboxylic acid {(1S)-[(S)-hydroxy-(methoxy-**methyl**-carbamoyl)-**methyl**]-2-phenyl-ethyl}-amide

DETD Aqueous 1N NaOH (2.6 mL) was added to a solution of (3S)-[(5-Chloro-1H-indole-2-carbonyl)amino]-(2S)-hydroxy-4-phenylbutyric acid **methyl** ester (500 mg, 1.29 mmol) in methanol at 25.degree. C. After 18 hours the mixture was concentrated, the residue dissolved. . .

DETD ((3S)-[(5-Chloro-1H-indole-2-carbonyl)-amino]-(2S)-hydroxy-4-phenyl-butyric acid **methyl** ester

DETD (3S)-Amino-(2S)-hydroxy-4-phenyl-butyric acid **methyl** ester (1.4 mmol) and 5-Chloro-1H-indole-2-carboxylic acid (1.37 mmol) were coupled according to Procedure A (0-25.degree. C. reaction, 40 hour reaction. . .

DETD (3S)-Amino-(2S)-hydroxy-4-phenyl-butyric acid **methyl** ester

DETD [1(S)-**Benzyl**-(2S)-(tert-butyl-dimethyl-silanyloxy)-2-cyano-ethyl]-carbamic acid tert-butyl ester (417 mg) was added to a solution of anhydrous HCl (3.2g) in methanol (20 mL) and the. . .

DETD [1(S)-**Benzyl**-(2S)-(tert-butyl-dimethyl-silanyloxy)-2-cyano-ethyl]-carbamic acid tert-butyl ester

DETD Aqueous 2N NaOH (375 mL) was added at 10-22.degree. C. to a solution of crude (3S)-[(5-chloro-1H-indole-2-carbonyl)-amino]-(2R)-hydroxy-4-phenylbutyric acid **methyl** ester (containing 13% of the N,O-bis-5-chloro-1H-indole-2-carbonyl impurity, 140.7 g, 363 mmol) in methanol (1900 mL) and the mixture was allowed. . .

DETD A solution of (3S)-[(5-fluoro-1H-indole-2-carbonyl)-amino]-(2R)-hydroxy-4-phenyl-butyric acid **methyl** ester (190 mg, 0.5 mmol), 1N NaOH (1 mL) and methanol (5 mL) was stirred at 25.degree. C. for 18. . .

DETD Aqueous 1N NaOH (60 mL) was added to a solution of (3S)-[(5-bromo-1H-indole-2-carbonyl)-amino]-(2R)-hydroxy-4-phenyl-butyric acid **methyl** ester (2.45 g, 5.7 mmol) in methanol (60 mL) at 25.degree. C. After 2 hours the mixture was concentrated and. . .

DETD Aqueous 1N NaOH (1.18 mL) was added to a suspension of (3S)-[(5,6-dichloro-1H-indole-2-carbonyl)-amino]-(2R)-hydroxy-4-phenyl-butyric acid **methyl** ester (249 mg, 0.6 mmol) in methanol (5 mL) at 25.degree. C. After 18 hours the mixture was concentrated, the. . .

DETD Aqueous 1N NaOH (1.69 mL) was added to a suspension of (3R)-[(5-Chloro-1H-indole-2-carbonyl)-amino]-(2R)-hydroxy-4-phenyl-butyric acid **methyl** ester (326 mg, 0.8 mmol) in methanol at 25.degree. C. After 2.5 hours the mixture was concentrated (starting

material found). . .

DETD (3R)-[(5-Chloro-1H-indole-2-carbonyl)-amino]-(2R)-hydroxy-4-phenyl-butyric acid **methyl** ester

DETD (2R,3R)-3-Amino-2-hydroxy-4-phenylbutyric acid **methyl** ester hydrochloride (239 mg, 1.0 mmol) and 5-chloro-1H-indole-2-carboxylic acid (200 mg, 1.05 mmol) were coupled according to Procedure A (0-25.degree.. . .

DETD (2R,3R)-3-Amino-2-hydroxy-4-phenylbutyric acid **methyl** ester Hydrochloride

DETD 5-Chloro-1H-indole-2-carboxylic acid [(2RS)-hydroxy-2-(methoxy-**methyl**-carbamoyl)-ethyl]-amide

DETD A large excess of anhydrous ammonia was introduced into a solution of (3S)-[(5-chloro-1H-indole-2-carbonyl)-amino]-(2R)-hydroxy-4-phenylbutyric acid **methyl** ester (100 mg, 0.27 mmol) in methanol (10 mL) and the mixture was heated in a stainless steel Parr reactor. . .

DETD 5,6-Dichloro-1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(methoxy-**methyl**-carbamoyl)-**methyl**]-2-phenyl-ethyl}-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid [(1S)-((R)-hydroxy-dimethylcarbamoyl-**methyl**)-2-phenyl-ethyl]-amid

DETD 5-Chloro-1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(hydroxy-**methyl**-carbamoyl)-**methyl**]-2-phenyl-ethyl}-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid [(1S)-((R)-hydroxy-methoxycarbamoyl-**methyl**)-2-phenyl-ethyl]-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(methoxy-**methyl**-carbamoyl)-**methyl**]-2-phenyl-ethyl}-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid (2S)-[(5-chloro-1H-indole-2-carbonyl)-amino]-(1R)-(methoxy-**methyl**-carbamoyl)-3-phenyl-propyl ester

DETD (3S)-Amino-(2R)-hydroxy-N-methoxy-N-**methyl**-4-phenyl-butyramide hydrochloride (4.2 mmol) and 5-chloro-1H-indole-2-carboxylic acid (4.2 mmol) were coupled according to Procedure A. The mixture was purified by chromatography. . . silica eluting with 33-50% ethyl acetate-hexanes giving the title substance (100 mg) and the more polar major substance 5-chloro-1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(methoxy-**methyl**-carbamoyl)-**methyl**]-2-phenyl-ethyl}-amide (970 mg), plus a mixture of the two substances (159 mg, mostly more polar product). For the title substance: PBMS. . .

DETD 5-Chloro-1H-indole-2-carboxylic acid ((1S)-**benzyl**-(2R)-hydroxy-3-oxo-3-pyrrolidin-1-yl-propyl)-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-(2R)-hydroxy-3-(3-hydroxy-azetidin-1-yl)-3-oxo-propyl]-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid ((1S)-**benzyl**-(2R)-hydroxy-3-isoxazolidin-2-yl-3-oxo-propyl)-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid [(1S)-((R)-diethylcarbamoyl-hydroxy-**methyl**)-2-phenyl-ethyl]-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid ((1S)-{(R)-hydroxy-[(2-hydroxy-ethyl)-**methyl**-carbamoyl]-**methyl**}-2-phenyl-ethyl)-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid ((1S)-**benzyl**-(2R)-hydroxy-3-oxo-3-piperidin-1-yl-propyl)-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid ((1S)-**benzyl**-2(R)-hydroxy-3-morpholin-4-yl-3-oxo-propyl)-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid ((1S)-**benzyl**-(2R)-hydroxy-3-[1,2]oxazinan-2-yl-3-oxo-propyl)-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-(2R)-hydroxy-3-((3S)-hydroxy-pyrrolidin-1-yl)-3-oxo-propyl]-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid [(1S)-((R)-tert-butoxycarbamoyl-hydroxy-**methyl**)-2-phenyl-ethyl]-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid ((1S)-**benzyl**-(2R)-hydroxy-3-oxo-3-thiazolidin-3-yl-propyl)-amide

DETD **Thiazolidine** (0.70 mmol) and (3S)-[(5-chloro-1H-indole-2-

carbonyl)-amino]-(2R)-hydroxy-4-phenyl-butyric acid (0.67 mmol) were coupled according to Procedure A (1:1-dichloromethane-dimethylformamide solvent) giving product which was used. . .

DETD 5-Bromo-1H-indole-2-carboxylic acid [(1S)-((R)-dimethylcarbamoyl-hydroxy-**methyl**)-2-phenyl-ethyl]-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(pyridin-3-ylcarbamoyl)-**methyl**]-2-phenyl-ethyl}-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(2,2,2-trifluoro-ethylcarbamoyl)-**methyl**]-2-phenyl-ethyl}-amide

DETD (S)-5-Chloro-1H-indole-2-carboxylic acid [1-(methoxy-**methyl**-carbamoanecarbonyl)-2-phenyl-ethyl]-amide

DETD 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (DEC, 790 mg, 4.12 mmol), dichloroacetic acid (136 mg, 1.06 mmol) and 5-chloro-1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(methoxy-**methyl**-carbamoyl)-**methyl**]-2-phenyl-ethyl}-amide (287 mg, 0.69 mmol) were added, in this order, to a solution of anhydrous dimethylsulfoxide (4 mL) and toluene (anhydrous,. . .

DETD 5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-(2R)-hydroxy-3-(4-hydroxy-Piperidin-1-yl)-3-oxo-propyl]-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-(2R)-hydroxy-3-((3R,S)-hydroxy-piperidin-1-yl)-3-oxo-propyl]-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-(2R)-hydroxy-3-((2R)-hydroxymethyl-pyrrolidin-1-yl)-3-oxo-propyl]-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid ((1S)-{(R)-[(2-dimethylaminoethyl)-**methyl**-carbamoyl]-hydroxy-**methyl**}-2-phenyl-ethyl)-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-3-((3R,4R)-dihydroxy-pyrrolidin-1-yl)-2R-hydroxy-3-oxo-propyl]-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-3-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)-hydroxy-3-oxo-propyl]-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-3-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)-hydroxy-3-oxo-propyl]-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid ((1S)-**benzyl**-(2R)-hydroxy-3-oxo-3-thiomorpholin-4-yl-propyl)-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(**methyl**-pyridin-2-yl-carbamoyl)-**methyl**]-2-phenyl-ethyl}-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-3-(4-formylpiperazin-1-yl)-(2R)-hydroxy-3-oxo-propyl]-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-(2R)-hydroxy-3-(4-hydroxymethyl-piperidin-1-yl)-3-oxo-propyl]-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid ((1S)-{(R)-hydroxy-[**methyl**-(2-pyridin-2-yl-ethyl)-carbamoyl]-**methyl**}-2-phenyl-ethyl)-amide

DETD **Methyl**-(2-pyridin-2-yl-ethyl)-amine (0.77 mmol) and (3S)-[(5-chloro-1H-indole-2-carbonyl)-amino]-(2R)-hydroxy-4-phenyl-butyric acid (0.70 mmol) were coupled according to Procedure A (dimethylformamide solvent) and the product purified by. . .

DETD 5-Chloro-1H-indole-2-carboxylic acid {(1R)-[(S)-hydroxy-(methoxy-**methyl**-carbamoyl)-**methyl**]-2-phenyl-ethyl}-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid (0.25 mmol) and (2S,3R)-3-amino-2-hydroxy-N-methoxy-N-**methyl**-4-phenyl-butyramide hydrochloride (0.25 mmol) were coupled according to Procedure A (0-25.degree. C. acid then base wash). The crude product was dissolved. . .

DETD (2S,3R)-3-amino-2-hydroxy-N-methoxy-N-**methyl**-4-phenyl-butyramide hydrochloride

DETD {1(R)-[Hydroxy-((S)-methoxy-**methyl**-carbamoyl)-**methyl**]-2-phenyl-ethyl}-carbamic acid (285 mg, 0.8 mmol) was dissolved in cold 4N HCl-dioxane and the resulting solution stirred for 1 hour at. . .

DETD {(1S)-[Hydroxy-((R)-methoxy-**methyl**-carbamoyl)-**methyl**]-2-phenyl-ethyl}-carbamic acid

DETD 5-Chloro-1H-indole-2-carboxylic acid {(1 R)-[hydroxy-((R)-methoxy-

methyl-carbamoyl)-**methyl**]-2-phenyl-ethyl}-amide

DETD 5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-(2R)-hydroxy-3-oxo-3-(1-oxo-1-thiazolidin-3-yl)-propyl]-amide

DETD m-Chloroperoxybenzoic acid (62 mg of 50%, 0.18 mmol) was added at 25.degree. C. to a solution of 5-chloro-1H-indole-2-carboxylic acid ((1S)-**benzyl**-(2R)-hydroxy-3-oxo-3-thiazolidin-3-yl-propyl)-amide (80 mg, 0.18 mmol) in dichloromethane (2 mL). After 1 hour the mixture was poured into a mixture of saturated. . .

DETD 5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-(2R)-hydroxy-3-oxo-3-(1-oxo-1-thiomorpholin-4-yl)-propyl]-amide (Example 70)

DETD 5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-3-(1,1-dioxo-1-thiomorpholin-4-yl)-(2R)-hydroxy-3-oxo-propyl]-amide (Example 71)

DETD m-Chloroperoxybenzoic acid (45 mg of 50%, 0.13 mmol) was added at 25.degree. C. to a solution of 5-chloro-1H-indole-2-carboxylic acid ((1S)-**benzyl**-(2R)-hydroxy-3-oxo-3-thiomorpholin-4-yl-propyl)-amide (60 mg, 0.13 mmol) in dichloromethane (1.5 mL). After 1 hour the mixture was poured into a mixture of saturated. . .

DETD 5-Chloro-1H-indole-2-carboxylic acid [(1S)-((R)-hydroxy-hydroxycarbamoyl-**methyl**)-2-phenyl-ethyl]-amide

DETD Trifluoroacetic acid (2 mL) was added to a solution of 5-chloro-1H-indole-2-carboxylic acid [(1S)-((R)-tert-butoxycarbamoyl-hydroxy-**methyl**)-2-phenyl-ethyl]-amide (256 mg, 0.58 mmol) in dichloromethane (2 mL) and the resulting solution was stirred for 18 hours at 25.degree. C.. . .

DETD 5-Chloro-1H-indole-2-carboxylic acid ((1S)-{[(**benzyl**-piperidin-4-yl)-**methyl**-carbamoyl]-(R)-hydroxy-**methyl**}-2-phenyl-ethyl)-amide

DETD (3S)-[(5-Chloro-1H-indole-2-carbonyl)amino]-(2R)-hydroxy-4-phenylbutyric acid (310 mg, 0.8 mmol) and (1-**benzyl**-piperidin4-yl)-**methyl**-amine hydrochloride (EPO publication 0 457 686, example 1A therein, 200 mg, 0.8 mmol) were coupled according to Procedure A (dimethylformamide. . .

DETD 4-({(3S)-[(5-Chloro-1H-indole-2-carbonyl)-amino]-(2R)-hydroxy-4-phenyl-butyryl}-**methyl**-amino)-piperidine-1-carboxylic acid tert-butyl ester

DETD 5-Chloro-1H-indole-2-carboxylic acid {(1-S)[(R)-hydroxy-(**methyl**-piperidin-4-yl-carbamoyl)-**methyl**]-2-phenyl-ethyl}-amide hydrochloride

DETD 4-({(3S)-[(5-Chloro-1H-indole-2-carbonyl)-amino]-(2R)-hydroxy-4-phenyl-butyryl}-**methyl**-amino)-piperidine-1-carboxylic acid tert-butyl ester (292 mg, 0.5 mmol) was dissolved in 4M HCl-dioxane at 0.degree. C. and stirred for 1 hour. . .

DETD 5-Chloro-1H-indole-2-carboxylic acid ((1S)-{(R)-hydroxy-[**methyl**-(1-**methyl**-piperidin-4-yl)-carbamoyl]-**methyl**}-2-phenyl-ethyl)-amide hydrochloride

DETD . . . aqueous formaldehyde (37 weight % in water, 22 mg, 0.3 mmol) were added sequentially to a solution of 5-chloro-1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(**methyl**-piperidin4-yl-carbamoyl)-**methyl**]-2-phenyl-ethyl}-amide hydrochloride (100 mg, 0.2 mmol) in methanol (2 mL) at 25.degree. C. After 18 hours the reaction mixture was filtered. . .

DETD (3S)-[(5-Chloro-1H-indole-2-carbonyl)-amino]-4-phenyl-butyric acid **methyl** ester

DETD (3S)-3-Amino4-phenyl-butyric acid **methyl** ester hydrochloride (1.15 g, 5 mmol) and 5-chloro-1H-indole-2-carboxylic acid were coupled according to procedure A. The product was purified by. . .

DETD (3S)-Amino4-phenyl-butyric acid **methyl** ester hydrochloride

DETD (3S)-tert-Butoxycarbonylamino-4-phenyl-butyric acid **methyl** ester (ref. Heterocycles, p. 1835 (1989) and J. Med. Chem. 1975, p. 761, 3.49 g, 12.1 mmol) was dissolved in. . .

CLM What is claimed is:

. . . (C.sub.1 -C.sub.4)alkyl, (C.sub.1 -C.sub.4)alkoxy, fluoromethyl, difluoromethyl or trifluoromethyl; R.sub.2 is H; R.sub.3 is H or (C.sub.1 -C.sub.5)alkyl; R.sub.4 is H, **methyl**, ethyl, n-propyl, hydroxy(C.sub.1 -C.sub.3)alkyl, (C.sub.1 -C.sub.3)alkoxy(C.sub.1 -C.sub.3)alkyl, phenyl(C.sub.1 -C.sub.4)alkyl, phenylhydroxy(C.sub.1 -C.sub.4)alkyl, phenyl(C.sub.1 -C.sub.4)alkoxy(C.sub.1 -C.sub.4)alkyl, thien-2- or -3-yl(C.sub.1 -C.sub.4)alkyl or fur-2-. . . are independently phenyl, furyl or pyrrolidinyl wherein the nonaromatic nitrogen-containing R.sub.9 rings are optionally mono-substituted on nitrogen with (C.sub.1 -C.sub.6)alkyl, **benzyl**, benzoyl or (C.sub.1 -C.sub.6)alkoxycarbonyl and wherein the R.sub.9 rings are optionally mono-substituted on carbon with halo, (C.sub.1 -C.sub.4)alkyl, (C.sub.1 -C.sub.4)alkoxy,. . . -C.sub.4)alkylcarbamoyl, (C.sub.1 -C.sub.4)alkoxyimino, (C.sub.1 -C.sub.4)alkoxymethoxy, (C.sub.1 -C.sub.6)alkoxycarbonyl, carboxy(C.sub.1 -C.sub.5)alkyl or hydroxy(C.sub.1 -C.sub.5)alkyl; with the proviso that if R.sub.4 is H, **methyl**, ethyl or n-propyl, R.sub.5 is OH; with the proviso that if R.sub.5 and R.sub.7 are H, then R.sub.4 is not H, **methyl**, ethyl, n-propyl, hydroxy(C.sub.1 -C.sub.3)alkyl or (C.sub.1 -C.sub.3)alkoxy(C.sub.1 -C.sub.3)alkyl and R.sub.6 is C(O)NR.sub.8 R.sub.9, C(O)R.sub.12 or (C.sub.1 -C.sub.4)alkoxycarbonyl.

2. A compound as recited in claim 1 wherein R.sub.1 is 5-H, 5-halo, 5-**methyl**, 5-trifluoromethyl or 5-cyano; R.sub.10 and R.sub.11 are each independently H or halo; A is --C(H).dbd.; R.sub.2 and R.sub.3 are H;. . .

4. A compound as recited in claim 3 selected from 5-Chloro-1H-indole-2-carboxylic acid [(1S)-((R)-hydroxy-dimethylcarbamoyl-**methyl**)-2-phenyl-ethyl]-amide, 5,6-Dichloro-1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(methoxy-**methyl**-carbamoyl)-**methyl**]-2-phenyl-ethyl}-amide, 5-Chloro- 1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(methoxy-**methyl**-carbamoyl)-**methyl**]-2-phenyl-ethyl}-amide or 5-Chloro-1H-indole-2-carboxylic acid ((1S)-{(R)-hydroxy-[(2-hydroxy-ethyl)-**methyl**-carbamoyl]-**methyl**}-2-phenyl-ethyl)-amide.

5. The compound as recited in claim 3 wherein R.sub.1 is 5-chloro; R.sub.10 and R.sub.11 are H; R.sub.4 is **benzyl**; R.sub.8 is **methyl**; and R.sub.9 is **methyl**.

6. The compound as recited in claim 3 wherein R.sub.1 is 5-chloro; R.sub.11 is H; R.sub.10 is 6-chloro; R.sub.4 is **benzyl**; R.sub.8 is **methyl**; and R.sub.9 is methoxy.

7. The compound as recited in claim 3 wherein R.sub.1 is 5-chloro; R.sub.10 and R.sub.11 are H; R.sub.4 is **benzyl**; R.sub.8 is **methyl**; and R.sub.9 is methoxy.

8. The compound as recited in claim 3 wherein R.sub.1 is 5-chloro; R.sub.10 and R.sub.1 are H; R.sub.4 is **benzyl**; R.sub.8 is **methyl**; and R.sub.9 is 2-(hydroxy)ethyl.

10. A compound as recited in claim 1 selected from 5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-(2R)-hydroxy-3-((3S)-hydroxy-pyrrolidin-1-yl)-3-oxo-propyl]-amide, 5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-3-((3S,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)-hydroxy-3-oxo-propyl]-amide or 5-Chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-3-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)-hydroxy-3-oxo-propyl]-amide.

11. The compound as recited in claim 9 wherein R.sub.1 is 5-chloro; R.sub.10 and R.sub.11 are H; R.sub.4 is **benzyl**; and R.sub.12 is 3(S)-hydroxypyrrolidin-1-yl.

12. The compound as recited in claim 9 wherein R.sub.1 is 5-chloro; R.sub.10 and R.sub.11 are H; R.sub.4 is **benzyl**; and R.sub.12 is (3S,4S)-dihydroxypyrrolidin-1-yl.

13. The compound as recited in claim 9 wherein R.sub.1 is 5-chloro; R.sub.10 and R.sub.11 are H; R.sub.4 is **benzyl**; and R.sub.12 is (3R,4S)-dihydroxypyrrolidin-1-yl.

14. A compound as recited in claim 1 wherein R.sub.1 is H, halo, **methyl** or cyano; R.sub.10 and R.sub.11 are each independently H or halo; A is --C(H).dbd.; R.sub.2 and R.sub.3 are H; R.sub.4. . . . . 16. The compound as recited in claim 15 wherein R.sub.1 is 5-chloro; R.sub.10 and R.sub.11 are H; and R.sub.4 is **benzyl**.

17. A compound as recited in claim 1 wherein R.sub.1 is H, halo, **methyl** or cyano; R.sub.10 and R.sub.11 are each independently H or halo; A is --C(H).dbd.; R.sub.2 and R.sub.3 are H; R.sub.4. . .
18. A compound as recited in claim 1 wherein R.sub.1 is H, halo, **methyl** or cyano; R.sub.10 and R.sub.11 are each independently H or halo; A is --C(H).dbd.; R.sub.2 and R.sub.3 are H; R.sub.4. . .
21. The method as recited in claim 19 for treating **diabetes** in a mammal by administering to a mammal suffering from **diabetes** a therapeutically effective amount of a compound of claim 1.

. . . (C.sub.1 -C.sub.4)alkyl, (C.sub.1 -C.sub.4)alkoxy, fluoromethyl, difluoromethyl or trifluoromethyl; R.sub.2 is H; R.sub.3 is H or (C.sub.1 -C.sub.5)alkyl; R.sub.4 is H, **methyl**, ethyl, n-propyl, hydroxy(C.sub.1 -C.sub.3)alkyl, (C.sub.1 -C.sub.3)alkoxy(C.sub.1 -C.sub.3)alkyl, phenyl(C.sub.1 -C.sub.4)alkyl, phenylhydroxy(C.sub.1 -C.sub.4)alkyl, phenyl(C.sub.1 -C.sub.4)alkoxy(C.sub.1 C.sub.4)alkyl, thien-2- or -3-yl(C.sub.1 -C.sub.4)alkyl or fur-2-. . . are independently phenyl, furyl or pyrrolidinyl wherein the nonaromatic nitrogen-containing R.sub.9 rings are optionally mono-substituted on nitrogen with (C.sub.1 -C.sub.6)alkyl, **benzyl**, benzoyl or (C.sub.1 -C.sub.6)alkoxycarbonyl and wherein the R.sub.9 rings are optionally mono-substituted on carbon with halo, (C.sub.1 -C.sub.4)alkyl, (C.sub.1 -C.sub.4)alkoxy,. . . -C.sub.4)alkylcarbamoyl, (C.sub.1 -C.sub.4)alkoxyimino, (C.sub.1 -C.sub.4)alkoxymethoxy, (C.sub.1 -C.sub.6)alkoxycarbonyl, carboxy(C.sub.1 -C.sub.5)alkyl or hydroxy(C.sub.1 -C.sub.5)alkyl; with the proviso that if R.sub.4 is H, **methyl**, ethyl or n-propyl, R.sub.5 is OH; with the proviso that if R.sub.5 and R.sub.7 are H, then R.sub.4 is not H, **methyl**, ethyl, n-propyl, hydroxy(C.sub.1 -C.sub.3)alkyl or (C.sub.1 -C.sub.3)alkoxy(C.sub.1 -C.sub.3)alkyl and R.sub.6 is C(O)NR.sub.8 R.sub.9, C(O)R.sub.12 or (C.sub.1 -C.sub.4)alkoxycarbonyl.

. . . (C.sub.1 -C.sub.4)alkyl, (C.sub.1 -C.sub.4)alkoxy, fluoromethyl, difluoromethyl or trifluoromethyl; R.sub.2 is H; R.sub.3 is H or (C.sub.1 -C.sub.5)alkyl; R.sub.4 is H, **methyl**, ethyl, n-propyl, hydroxy(C.sub.1 -C.sub.3)alkyl, (C.sub.1 -C.sub.3)alkoxy(C.sub.1 -C.sub.3)alkyl, phenyl(C.sub.1 -C.sub.4)alkyl, phenylhydroxy(C.sub.1 -C.sub.4)alkyl, phenyl(C.sub.1 -C.sub.4)alkoxy(C.sub.1 -C.sub.4)alkyl, thien-2- or -3-yl(C.sub.1 -C.sub.4)alkyl or fur-2-. . . are independently phenyl, furyl or pyrrolidinyl wherein the nonaromatic nitrogen-containing R.sub.9 rings are optionally mono-substituted on nitrogen with (C.sub.1 -C.sub.6)alkyl, **benzyl**, benzoyl or (C.sub.1

-C.sub.6)alkoxycarbonyl and wherein the R.sub.9 rings are optionally mono-substituted on carbon with halo, (C.sub.1 -C.sub.4)alkyl, (C.sub.1 -C.sub.4)alkoxy,. . . -C.sub.4)alkylcarbamoyl, (C.sub.1 -C.sub.4)alkoxyimino, (C.sub.1 -C.sub.4)alkoxymethoxy, (C.sub.1 -C.sub.6)alkoxycarbonyl, carboxy(C.sub.1 -C.sub.5)alkyl or hydroxy(C.sub.1 -C.sub.5)alkyl; with the proviso that if R.sub.4 is H, **methyl**, ethyl or n-propyl, R.sub.5 is OH; with the proviso that if R.sub.5 and R.sub.7 are H, then R.sub.4 is not H, **methyl**, ethyl, n-propyl, hydroxy(C.sub.1 -C.sub.3)alkyl or (C.sub.1 -C.sub.3)alkoxy(C.sub.1 -C.sub.3)alkyl and R.sub.6 is C(O)NR.sub.8 R.sub.9, C(O)R.sub.12 or (C.sub.1 -C.sub.4)alkoxycarbonyl.

. . . (C.sub.1 -C.sub.4)alkyl, (C.sub.1 -C.sub.4)alkoxy, fluoromethyl, difluoromethyl or trifluoromethyl; R.sub.2 is H; R.sub.3 is H or (C.sub.1 -C.sub.5)alkyl; R.sub.4 is H, **methyl**, ethyl, n-propyl, hydroxy(C.sub.1 -C.sub.3)alkyl, (C.sub.1 -C.sub.3)alkoxy(C.sub.1 -C.sub.3)alkyl, phenyl(C.sub.1 -C.sub.4)alkyl, phenylhydroxy(C.sub.1 -C.sub.4)alkyl, phenyl(C.sub.1 -C.sub.4)alkoxy(C.sub.1 -C.sub.4)alkyl, thien-2- or -3-yl(C.sub.1 -C.sub.4)alkyl or fur-2-. . . said substituents are independently furyl or pyrrolidinyl wherein the nonaromatic nitrogen-containing R.sub.9 rings are mono-substituted on nitrogen with (C.sub.1 -C.sub.6)alkyl, **benzyl**, benzoyl or (C.sub.1 -C.sub.6)alkoxycarbonyl and wherein the R.sub.9 rings are optionally mono-substituted on carbon with halo, (C.sub.1 -C.sub.4)alkyl, (C.sub.1 -C.sub.4)alkoxy,. . . 2-(C.sub.1 -C.sub.6)alkoxycarbonylpyrrolidin-1-yl or 2(R)-hydroxymethylpyrrolidin-1-yl; or R.sub.12 is 3- and/or 4-, di-substituted pyrrolidin-1-yl with the proviso that if R.sub.4 is H, **methyl**, ethyl or n-propyl, R.sub.5 is OH; with the proviso that if R.sub.5 and R.sub.7 are H, then R.sub.4 is not H, **methyl**, ethyl, n-propyl, hydroxy(C.sub.1 -C.sub.3)alkyl or (C.sub.1 -C.sub.3)alkoxy(C.sub.1 -C.sub.3)alkyl and R.sub.6 is C(O)NR.sub.8 R.sub.9, C(O)R.sub.12 or (C.sub.1 -C.sub.4)alkoxycarbonyl.

37. A method for treating **diabetes** in a mammal by administering to a mammal suffering from **diabetes** a therapeutically effective amount of a compound of claim 30.

45. A method for treating Type I **diabetes** in a mammal which comprises administering to a mammal a therapeutically effective amount of a compound of claim 30.

46. A method as recited in claim 45 wherein the compound is 5-chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl** -3-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)-hydroxy-3-oxo-propyl]-amide.

47. A method for treating Type II **diabetes** in a mammal which comprises administering to a mammal a therapeutically effective amount of a compound of claim 30.

48. A method as recited in claim 47 wherein the compound is 5-chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl** -3-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)-hydroxy-3-oxo-propyl]-amide.

49. A method for treating Type II **diabetes** in a mammal which comprises administering to a mammal a therapeutically effective amount of a compound of claim 30.

50. A method as recited in claim 49 wherein the compound is 5-chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl** -3-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)-hydroxy-3-oxo-propyl]-amide.

52. A method as recited in claim 51 wherein the compound is 5-chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-3-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)-hydroxy-3-oxo-propyl]-amide.

54. A method as recited in claim 53 wherein the compound is 5-chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-3-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)-hydroxy-3-oxo-propyl]-amide.

56. A method as recited in claim 55 wherein the compound is 5-chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-3-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)-hydroxy-3-oxo-propyl]-amide.

58. A method as recited in claim 57 wherein the compound is 5-chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-3-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)-hydroxy-3-oxo-propyl]-amide.

60. A method as recited in claim 59 wherein the compound is 5-chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-3-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)-hydroxy-3-oxo-propyl]-amide.

62. A method as recited in claim 61 wherein the compound is 5-chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-3-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)-hydroxy-3-oxo-propyl]-amide.

64. A method as recited in claim 63 wherein the compound is 5-chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-3-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)-hydroxy-3-oxo-propyl]-amide.

66. A method as recited in claim 65 wherein the compound is 5-chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-3-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)-hydroxy-3-oxo-propyl]-amide.

67. A pharmaceutical composition which comprises a therapeutically effective amount of a.) 5-chloro-1H-indole-2-carboxylic acid [(1S)-**benzyl**-3-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)-hydroxy-3-oxo-propyl]-amide; b.) an antidiabetic agent selected from glypizide, **glimepiride**, repaglinide, metformin, pioglitazone, troglitazone, BRL49653 (rosiglitazone), acarbose and miglitol; and c.) optionally a pharmaceutically acceptable carrier.

69. A pharmaceutical composition as recited in claim 67 wherein the antidiabetic agent is **glimepiride**.

77. A pharmaceutical composition which comprises a therapeutically effective amount of a. 5-chloro-1H-indole-2-carboxylic acid[(1S)-**benzyl**-3-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-(2R)-hydroxy-3-oxo-propyl]amide, b. insulin; and c. optionally a pharmaceutically acceptable carrier.

L3 ANSWER 14 OF 15 USPATFULL on STN
AN 2000:1892 USPATFULL
TI Combinations for **diabetes**
IN Whitcomb, Randall Wayne, Ann Arbor, MI, United States
PA Warner-Lambert Company, Morris Plains, NJ, United States (U.S. corporation)
PI US 6011049 20000104
AI US 1998-189132 19981109 (9)
RLI Continuation-in-part of Ser. No. US 1997-970057, filed on 13 Nov 1997, now patented, Pat. No. US 5859037
PRAI US 1997-38224P 19970219 (60)
DT Utility

FS Granted
EXNAM Primary Examiner: Jordan, Kimberly
LREP Ashbrook, Charles W.
CLMN Number of Claims: 16
ECL Exemplary Claim: 1
DRWN 12 Drawing Figure(s); 12 Drawing Page(s)
LN.CNT 974
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Combinations of a glitazone antidiabetic agent and a biguanide antidiabetic agent, and optionally a sulfonylurea antidiabetic agent, are useful for treating **diabetes** mellitus and improving glycemic control.
TI Combinations for **diabetes**
AB . . . of a glitazone antidiabetic agent and a biguanide antidiabetic agent, and optionally a sulfonylurea antidiabetic agent, are useful for treating **diabetes** mellitus and improving glycemic control.
SUMM This invention relates to combinations of antidiabetic compounds, and to a method for treating **diabetes** employing such combinations.
SUMM **Diabetes** mellitus is a metabolic disorder characterized by hyperglycemia, insulin resistance, and is often associated with other disorders such as obesity,. . . class of compounds known as the glitazones has recently received a great deal of attention for their ability to treat **diabetes**. These compounds operate by increasing the sensitivity of insulin receptors throughout the body, thereby diminishing or eliminating the need for. . .
SUMM . . . using a combination comprised of a biguanide, a glitazone, and a sulfonylurea. Accordingly, such combinations are especially useful in treating **diabetes** and associated complications.
SUMM This invention provides a method of treating **diabetes** by administering to a subject in need of treatment a combination of a sulfonylurea antidiabetic agent and an antidiabetic glitazone,. . .
SUMM The sulfonylureas are a class of compounds that have been widely employed to treat **diabetes**. Such compounds are well known, for example as described in U.S. Pat. Nos. 3,454,635, 3,669,966, 2,968,158, 3,501,495, 3,708,486, 3,668,215, 3,654,357,. . . a heterocyclic group such as hexahydroazepine. Preferred sulfonylureas to be employed are those wherein A is chloro, alkyl such as **methyl**, or alkyl substituted with aryl carbonyl or aryl carboxamido, for instance 3-chloro-5-methoxybenzoylethyl or 5-**methyl**-2-pyrazinylcarbonylaminoethyl.
SUMM . . . sulfonylureas to be employed in the combinations of this invention are glyburide, gliquidone, glipizide, tolbutamide, tolazamide, glisoxepid, chlorpropamide, glibornuride, gliclazide, **glimepiride**, phenbutamide, and tolcyclamide.
SUMM According to this invention, the foregoing sulfonylureas are used in combination with a glitazone to treat **diabetes** and to improve glycemic control. The glitazones are a family of antidiabetic agents characterized as being thiazolidinediones or related analogs.. . .
SUMM 5-(4-[2-[1-(4-2'-Pyridylphenyl) ethylideneaminooxy]ethoxy]**benzyl**]-**thiazolidine**-2,4-dione;
SUMM 5-(4-[5-Methoxy-3-methylimidazo[5,4-b]pyridin-2-yl-methoxy) **benzyl**]-**thiazolidine**-2,4-dione, or its hydrochloride;
SUMM 5-[4-(6-Methoxy-1-methylbenzimidazol-2-yl-methoxy)**benzyl**]-**thiazolidine**-2,4-dione;
SUMM 5-[4-(1-Methylbenzimidazol-2-ylmethoxy) **benzyl**] **thiazolidine**-2,4-dione; and
SUMM 5-[4-(5-Hydroxy-1,4,6,7-tetramethylbenzimidazol-2-ylmethoxy) **benzyl**]-**thiazolidine**-2,4-dione.
DETD . . . glitazone is used in combination with a biguanide, or in combination with both a sulfonylurea and a biguanide, to treat **diabetes** and to improve glycemic control in patients in need of treatment. The compounds can be employed individually, or can be. . .

DETD . . . for example, metformin and a glitazone, as well as metformin, a sulfonylurea and a glitazone, and a method of treating **diabetes** and controlling glycemic conditions comprising administering to a patient in need of treatment an effective amount of metformin and a. . . 1000 to about one part by weight glitazone. For example, a typical composition of glyburide and troglitazone will contain about **12 mg** of glyburide and about 500 mg of troglitazone. Such combination will be administered to an adult patient about once each. . . will be about 500 mg of metformin and about 300 to 600 mg of troglitazone. A typical three-way composition includes **12 mg** of glyburide, 400 mg of troglitazone, and 500 mg of metformin.

DETD The method of treating **diabetes** employing a combination provided by this invention has been established in a long-term controlled clinical evaluation. A typical study determined. . . the efficacy and safety of troglitazone alone and in combination with the sulfonylurea glyburide for the treatment of non-insulin dependent **diabetes** mellitus (NIDDM). This study targeted the segment of the NIDDM population in which the disease state has progressed to a. . .

DETD . . . and Drug Administration has now approved the use of troglitazone in combination with sulfonylureas in the treatment of type II **diabetes**. Troglitazone is now routinely used clinically in combination with sulfonylureas, especially glyburide. A brief summary of the results of the. . .

DETD . . . on troglitazone (3 patients; two on 400 mg, one on 600 mg) or troglitazone combination (4 patients; three on 400 mg/**12 mg**, one on 600 mg/**12 mg**). Eight patients had slight decreases within the normal range or were near the lower normal limit at baseline and dropped. . .

DETD . . . of one of the agents, the pathophysiology of the disease should be considered. Treating the basic defect of type II **diabetes**, i.e., insulin resistance, should take precedence over exhausting pancreatic insulin secretion by sulfonylurea stimulation. Therefore, as glycemic control improves the. . .

DETD . . . pressure at the end of the study. Mean diastolic blood pressure, however, decreased significantly ($p<0.05$) for patients treated with 600 mg/**12 mg** combination therapy. A reduction in diastolic BP is consistent with similar observation in other troglitazone studies. The direction and magnitude. . .

DETD In summary, patients with type II **diabetes** receiving maximum doses of sulfonylurea have very few oral therapeutic options remaining. Aside from insulin resistance, the hallmark of the. . .

DETD Troglitazone/glyburide combination therapy is well-tolerated and significantly ($p<0.0001$) improves glycemic control over a 52-week period at doses of 200 mg/**12 mg** to 600 mg/**12 mg** compared with glyburide monotherapy in patients with NIDDM who are not adequately controlled on sulfonylurea therapy.

DETD . . . as rosiglitazone, "RSG"), has undergone clinical evaluation and has demonstrated good efficacy in controlling glycemia in patients with type II **diabetes**. Rosiglitazone was evaluated in a multi-center, placebo-controlled trial. In this study, 493 patients with a fasting glucose between 7.8 mmol/L. . .

DETD . . . .+-. SD

58.8 .+-. 10.9

59.6 .+-. 9.8

60.7 .+-. 9.5

Range	36-81	39-79	38-80
Sex			
Males	104	107	113
Females	54	59	56
Duration of			

Diabetes (years)			
Mean	4.6	4.8	5.4
Previous Therapy			
Diet only	45	44	45
Previous oral agents	113	122	124
FPG.sup.a (mmol/L)			
Mean .+-. SD	12.7 .+-. 3.3		

. . .

DETD Several studies have been conducted showing the beneficial effects of pioglitazone, "Pi", ((.+-.)-5-[p-[2-(5-ethyl-2-**pyridyl**)ethoxy] **benzyl**]-2,4-thiazolidinedione hydrochloride), both alone and in combination with sulfonylureas, in controlling and promoting hepatic glucose uptake in patients having NIDDM. One. . .

DETD . . . have been shown to enhance hepatic and peripheral glucose uptake in animals, including humans, and are thus useful for treating **diabetes** mellitus. All of the glitazone compounds operate by the same mechanism within an animal system. Several studies have established the. . .

DETD . . . the dramatic reduction in plasma glucose levels. The combinations are thus particularly well suited to the treatment of type 2 **diabetes**, and can be utilized in the treatment of impaired glucose tolerance in order to even prevent or delay the onset. . .

CLM What is claimed is:

. . . mg to about 2000 mg of a biguanide antidiabetic agent, said amounts being synergistic in the treatment of non-insulin dependent **diabetes** mellitus.

7. A method of treating **diabetes** by administering to a patent in need of treatment from about 3 mg to about 250 mg of a sulfonylurea. . . to about 2000 mg of a biguanide antidiabetic agent, wherein said amounts are synergistic for the treatment of non-insulin dependent **diabetes** mellitus.

14. A method of treating **diabetes** by administering to a patient in need of treatment from about 5 mg to about 10 mg of rosiglitazone together. . . 3 mg to about 250 mg of a sulfonylurea, wherein said amounts are synergistic for the treatment of non-insulin dependent **diabetes** mellitus.

15. A method of treating **diabetes** by administering to a patient in need of treatment from about 100 mg to about 1000 mg of troglitazone together. . . 3 mg to about 250 mg of a sulfonylurea, wherein said amounts are synergistic for the treatment of non-insulin dependent **diabetes** mellitus.

16. A method of treating **diabetes** by administering to a patient in need of treatment from about 50 mg to about 200 mg of pioglitazone together. . . 3 mg to about 250 mg of a sulfonylurea, wherein said amounts are synergistic for the treatment of non-insulin dependent **diabetes** mellitus.

L3 ANSWER 15 OF 15 USPATFULL on STN
AN 1999:132855 USPATFULL
TI Sulfonylurea-glitazone combinations for **diabetes**
IN Whitcomb, Randall Wayne, Ann Arbor, MI, United States
PA Warner-Lambert Company, Morris Plains, NJ, United States (U.S. corporation)
PI US 5972973 19991026
AI US 1998-173911 19981016 (9)

RLI Continuation-in-part of Ser. No. US 1997-970057, filed on 13 Nov 1997, now patented, Pat. No. US 5859037
PRAI US 1997-38224P 19970219 (60)
DT Utility
FS Granted
EXNAM Primary Examiner: Jordan, Kimberly
LREP Ashbrook, Charles W.
CLMN Number of Claims: 6
ECL Exemplary Claim: 1
DRWN 7 Drawing Figure(s); 7 Drawing Page(s)
LN.CNT 733
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Combinations of a sulfonylurea antidiabetic agent and a glitazone antidiabetic agent are useful for treating **diabetes** mellitus and improving glycemic control.
TI Sulfonylurea-glitazone combinations for **diabetes**
AB Combinations of a sulfonylurea antidiabetic agent and a glitazone antidiabetic agent are useful for treating **diabetes** mellitus and improving glycemic control.
SUMM This invention relates to combinations of antidiabetic sulfonylurea compounds with glitazone compounds, and to a method for treating **diabetes** employing such combinations.
SUMM **Diabetes** mellitus is a metabolic disorder characterized by hyperglycemia, insulin resistance, and is often associated with other disorders such as obesity,. . . class of compounds known as the glitazones has recently received a great deal of attention for their ability to treat **diabetes**. These compounds operate by increasing the sensitivity of insulin receptors throughout the body, thereby diminishing or eliminating the need for. . .
SUMM . . . a sulfonylurea and a glitazone results in dramatic improvement in glycemic control. Accordingly, such combinations are especially useful in treating **diabetes** and associated complications.
SUMM This invention provides a method of treating **diabetes** by administering to a subject in need of treatment a combination of a sulfonylurea antidiabetic agent and an antidiabetic glitazone.
SUMM The sulfonylureas are a class of compounds that have been widely employed to treat **diabetes**. Such compounds are well known, for example as described in U.S. Pat. Nos. 3,454,635, 3,669,966, 2,968,158, 3,501,495, 3,708,486, 3,668,215, 3,654,357,. . . a heterocyclic group such as hexahydroazepine. Preferred sulfonylureas to be employed are those wherein A is chloro, alkyl such as **methyl**, or alkyl substituted with aryl carbonyl or aryl carboxamido, for instance 3-chloro-5-methoxybenzoylethyl or 5-**methyl**-2-pyrazinylcarbonylaminoethyl.
SUMM . . . sulfonylureas to be employed in the combinations of this invention are glyburide, gliquidone, glipizide, tolbutamide, tolazamide, glisoxepid, chlorpropamide, glibornuride, gliclazide, **glimepiride**, phenbutamide, and tolcyclamide.
SUMM According to this invention, the foregoing sulfonylureas are used in combination with a glitazone to treat **diabetes** and to improve glycemic control. The glitazones are a family of antidiabetic agents characterized as being thiazolidinediones or related analogs.. . .
SUMM 5-(4-[2-[1-(4-2'-Pyridylphenyl)ethylideneaminooxy]-ethoxy]**benzyl**]**thiazolidine**-2,4-dione;
SUMM 5-(4-[5-Methoxy-3-methylimidazo[5 ,4-b]pyridin-2-yl-methoxy) **benzyl**]**thiazolidine**-2,4-dione, or its hydrochloride;
SUMM 5-[4-(6-Methoxy-1-methylbenzimidazol-2-yl-methoxy)**benzyl**] **thiazolidine**-2,4-dione;
SUMM 5-[4-(1-Methylbenzimidazol-2-ylmethoxy)**benzyl**] **thiazolidine**-2,4-dione; and
SUMM 5-[4-(5-Hydroxy-1,4,6,7-tetramethylbenzimidazol-2-ylmethoxy) **benzyl**]**thiazolidine**-2,4-dione.

DETD According to this invention, a sulfonylurea is used in combination with a glitazone to treat **diabetes** and to improve glycemic control in patients in need of treatment. The compounds can be employed individually or can be. . .

DETD . . . be employed at doses of about 50 mg to about 200 mg per day. Another typical composition will comprise about **12 mg** of glyburide and about 5 mg of rosiglitazone. Another composition is 50 mg of pioglitazone and 5 mg of glyburide.

DETD The invention provides compositions of a sulfonylurea and a glitazone, and a method of treating **diabetes** and controlling glycemic conditions comprising administering to a patient in need of treatment an effective amount of a sulfonylurea and. . . 1000 to about one part by weight glitazone. For example, a typical composition of glyburide and troglitazone will contain about **12 mg** of glyburide and about 500 mg of troglitazone. Such combination will be administered to an adult patient about once each. . .

DETD The method of treating **diabetes** employing a combination of a sulfonylurea and a glitazone has been established in a long-term controlled clinical evaluation. The study. . . the efficacy and safety of troglitazone alone and in combination with the sulfonylurea glyburide for the treatment of non-insulin dependent **diabetes** mellitus (NIDDM). This study targeted the segment of the NIDDM population in which the disease state has progressed to a. . .

DETD . . . and Drug Administration has now approved the use of troglitazone in combination with sulfonylureas in the treatment of type II **diabetes**. Troglitazone is now routinely used clinically in combination with sulfonylureas, especially glyburide. A brief summary of the results of the. . .

DETD . . . on troglitazone (3 patients; two on 400 mg, one on 600 mg) or troglitazone combination (4 patients; three on 400 mg/**12 mg**, one on 600 mg/**12 mg**). Eight patients had slight decreases within the normal range or were near the lower normal limit at baseline and dropped. . .

DETD . . . of one of the agents, the pathophysiology of the disease should be considered. Treating the basic defect of type II **diabetes**, i.e., insulin resistance, should take precedence over exhausting pancreatic insulin secretion by sulfonylurea stimulation. Therefore, as glycemic control improves the. . .

DETD . . . pressure at the end of the study. Mean diastolic blood pressure, however, decreased significantly ($p<0.05$) for patients treated with 600 mg/**12 mg** combination therapy. A reduction in diastolic BP is consistent with similar observation in other troglitazone studies. The direction and magnitude. . .

DETD In summary, patients with type II **diabetes** receiving maximum doses of sulfonylurea have very few oral therapeutic options remaining. Aside from insulin resistance, the hallmark of the. . .

DETD Troglitazone/glyburide combination therapy is well-tolerated and significantly ($p<0.0001$) improves glycemic control over a 52-week period at doses of 200 mg/**12 mg** to 600 mg/**12 mg** compared with glyburide monotherapy in patients with NIDDM who are not adequately controlled on sulfonylurea therapy.

DETD . . . as rosiglitazone, "RSG"), has undergone clinical evaluation and has demonstrated good efficacy in controlling glycemia in patients with type II **diabetes**. Rosiglitazone was evaluated in a multi-center, placebo-controlled trial. In this study, 493 patients with a fasting glucose between 7.8 mmol/L. . .

DETD . . . SD 58.8 .+-. 10.9

59.6 .+-. 9.8

60.7 .+-. 9.5

Range	36-81	39-79	38-80
Sex			
Males	104	107	113

Females	54	59	56
Duration of **Diabetes** (years)			
Mean	4.6	4.8	5.4
Previous Therapy			
Diet only	45	44	45
Previous oral agents	113	122	124
FPG.sup.a (mmol/L)			
Mean .+-. SD	12.7 .+-. 3.3	12.6. . .	

DETD Several studies have been conducted showing the beneficial effects of pioglitazone ((.+-.)-5-[p-[2-(5-ethyl-2-**pyridyl**)ethoxy] **benzyl**]-2,4-thiazolidinedione hydrochloride), both alone and in combination with sulfonylureas, in controlling and promoting hepatic glucose uptake in patients having NIDDM. One. . .

DETD . . . have been shown to enhance hepatic and peripheral glucose uptake in animals, including humans, and are thus useful for treating **diabetes** mellitus. All of the glitazone compounds operate by the same mechanism within an animal system. Several studies have established the. . .

DETD . . . the dramatic reduction in plasma glucose levels. The combinations are thus particularly well suited to the treatment of type 2 **diabetes**, and can be utilized in the treatment of impaired glucose tolerance in order to even prevent or delay the onset. . .

CLM What is claimed is:

. . . about 50 mg of rosiglitazone (BRL49653), said amounts of sulfonylurea and rosiglitazone being synergistic for the treatment of non-insulin dependent **diabetes** mellitus in humans.

4. A method of treating non-insulin dependent **diabetes** mellitus in humans comprising administering to a patient in need of treatment from about 3 mg to about 250 mg. . . to about 50 mg of rosiglitazone, said amounts of sulfonylurea and rosiglitazone being synergistic for the treatment of non-insulin dependent **diabetes** mellitus in humans.

6. A method of treating non-insulin dependent **diabetes** mellitus in humans comprising administering to a patient in need of treatment from about 3 mg to about 250 mg. . . to about 10 mg of rosiglitazone, said amounts of sulfonylurea and rosiglitazone being synergistic for the treatment of non-insulin dependent **diabetes** mellitus in humans.